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Ashesh Piyush Shah · Cataldo Doria
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Contemporary Pancreas and Small Bowel Transplantation

Springer

Organ and Tissue Transplantation

Series Editor
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Editors

Contemporary Pancreas and Small Bowel Transplantation

With 140 Figures and 46 Tables

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Preface

Intestinal transplantation remains an intensive and taxing endeavor for both the patient and the clinical team. Yet, for the successful recipient, it is life-altering. Since its introduction, it has blossomed into a mainstream treatment modality for patients with intestinal failure. Unfortunately, access to intestinal transplantation is uneven. Many patients in need of intestinal transplantation have either difficult-to-treat disease processes or suffer catastrophic abdominal events. Unfortunately, many of these patients are never referred to centers specializing in intestinal failure and rehabilitation. Worse, many patients are told there is little that can be done. As a consequence, they often suffer from the complications associated with intestinal failure and indwelling catheters. Historically, much of this nihilism was due to a lack of exposure to intestinal transplantation or the outcomes after intestinal transplantation in the early era. Historical survival rates were fairly low, but as intestinal transplantation has matured as a field, the survival rates have climbed. In addition, there is a wealth of data regarding the improved quality of life associated with total parenteral nutrition (TPN) independence. This volume hopes to reintroduce the reader to the modern era of intestinal transplantation and the patients it may serve.

Pancreas transplant remains in the background despite major improvements in technique and overall survival coupled with a concomitant decrease in complications. Despite its relatively early origin in 1966 at the University of Minnesota, pancreas organ transplant volumes remain low as does its notoriety and prestige. Multiple factors have contributed to this: longer operative time vs kidney transplant, relatively lower reimbursement for the associated workload, more serious complications, and increased difficulty of monitoring, to name a few. Yet, despite the negative attributes pancreas transplant is given, the overall results continue to improve.

Since the first pancreas transplant performed in 1966, we have seen progressive improvement in patient and graft survival. While we are still far from the islet cell cure for all patients with diabetes, solid-organ whole-pancreas transplant remains the preferred transplant route for these patients with diabetes with secondary complications. That said, exciting work from the likes of one of our authors, Dr. Marvin Levy, has helped many patients receive their own islet cells to keep them from developing diabetes mellitus (DM) due to their chronic pancreatitis. Those of us who manage the ravaging secondary complications of patients with DM see firsthand the chronic and debilitating

path they are on. While a successful pancreas transplant will not reverse the secondary complications, it will delay the rapid progression of the secondary complications, and some state amelioration of diabetic changes in the native kidney is noted. At the very least, for the brittle diabetic, with a poor expectant quality of life, their life is impacted positively with a successful pancreas transplant.

Despite the positive overall results, gone are the days of transplant programs performing large volume of pancreas transplants on a yearly basis. In the 1990s, multiple transplant programs, such as the University of Minnesota and Maryland, routinely performed greater than 50 pancreas transplants per year. Today, it is rare to see any program perform more than 40 pancreas transplants per year. This has led to the vast majority of pancreas transplant programs being classified as "functionally inactive" at one time with the regulatory consequences that follow this designation. Also, this has led to fewer and fewer experienced pancreas transplant centers and personnel with potentially increased issues that come with decreased experience.

While islet cell transplant is closer to becoming a reality for patients with diabetes with secondary complications, solid-organ whole-pancreas transplant remains the gold standard for patients undergoing transplant. We hope that the following chapters written by some of the premier pancreas transplant physicians in the country will inform, educate, enlighten, and help in the management of these patients. Patients with diabetes mellitus present with some of the most devastating complications, and where experience and technology intersect with respect to pancreas transplant being a resource, this is the goal of our chapters.

Ashesh Piyush Shah
Cataldo Doria
James W. Lim, M.D., FACS.

Contents

About the Editors

Ashesh Piyush Shah is an Assistant Professor of Surgery at Thomas Jefferson University and the Surgical Director of Kidney Transplantation for the Jefferson Transplant Institute. He is board-certified in general surgery. Dr. Shah earned his medical degree at the Indiana University School of Medicine. He remained at Indiana University to complete his general surgery training. He completed his Multi-organ Abdominal Transplant Fellowship at Indiana University, training in liver, kidney, pancreas, and intestinal transplantation.

Dr. Cataldo Doria graduated Magna cum Laude from the University of Perugia, Italy, in 1990, where he was, also, resident in surgery from 1990 to 1995. He completed a research fellowship in small bowel transplantation at the University of Pittsburgh Transplantation Institute and a clinical fellowship in multi-organ transplantation at the Thomas E. Starzl Transplantation Institute of the University of Pittsburgh. Dr. Doria has Ph.D. in surgery biotechnology and transplant immunology and M.B.A.

Cataldo Doria, M.D., Ph.D., M.B.A., is the Cancer Center Medical Director at Capital Health in Pennington, NJ.

Prior to joining Capital Health, Dr. Doria was Professor of Surgery at Sidney Kimmel Medical College at Thomas Jefferson University in Philadelphia, PA. Dr. Doria is the inaugural Nicoletti Family Professor of Transplant Surgery at Sidney Kimmel Medical College, Thomas Jefferson University Hospital. He is also the Director of the Jefferson Transplant Institute, the Director of the Division of Transplantation, and the Surgical-Director of the Jefferson Kimmel Cancer Center, Liver Tumor Center, at the same institution. Dr. Doria is the Chairman of the Quality Assurance Performance Improvement Committee of the Jefferson Transplant Institute at Thomas Jefferson University Hospital. He is a multi-organ transplant surgeon who has extensive expertise in cadaveric and living-related liver and kidney transplant, pancreas transplant, small bowel transplant, as well as hepatobiliary and robotic surgery.

Prior to Jefferson, Dr. Doria was at the Mediterranean Institute for Transplantation and Advanced Specialized Therapies (ISMETT, UPMC Italy) – a partnership between the University of Pittsburgh Medical Center and the Italian National Government – where he served as Chief of Abdominal Organ Transplant. He also served as Assistant Professor of Surgery at the University of Pittsburgh School of Medicine and at the Thomas E. Starzl Transplantation Institute, Children's Hospital of Pittsburgh, and the US Department of Veterans Affairs Medical Center of Pittsburgh, PA.

His research interest focuses primarily on cancer of the liver, pancreas, and bile duct. Dr. Doria's biography has been listed in *Who's Who in Medicine and Healthcare*, *Who's Who in Finance and Industry*, *Who's Who in Science and Engineering*, and *Who's Who in America*. Dr. Doria, in year 2005, was named Honorary President of the Italian Association for Organ Donation of the Province of Taranto, Italy. In 2008, he was named "Surgeon of the Year" by the Mid-Atlantic Division of the American Liver Foundation. In 2009, he was the recipient of the Career Achievement Award by the International Association "Pugliesi nel Mondo." In 2010, he was awarded with the seal of the University of Foggia, Italy. In 2012, he was named "Knight of the Italian Republic" by the President of the Italian Republic. In 2016, he was named Chairman, Board of Directors, American Liver Foundation, Mid-Atlantic Division. Doria authored 277 scientific publications. Dr. Doria is a member of numerous professional and scientific societies wherein he has covered several official positions. Most importantly, Aldo has been, for the past 10 years, the leader of one of the most successful transplant institutes in North America and now leads one of the rising stars' cancer center in the northeast of the United States. Dr. Doria's plans include making Capital Health the most competitive and innovating cancer center of the East Coast of the United States.

James W. Lim Transplant Center, Porter Adventist Hospital, Denver, CO, USA

Dr. James W. Lim was born in South Korea but grew up in St. Louis, MO, attending the University of Missouri at Kansas City's 6-Year Medical Program immediately after high school. From the Midwest, he went to Philadelphia, PA, for his general surgery residency at Albert Einstein Medical Center, where he was recruited to join their fellowship program in Transplant Surgery upon completion of his residency. This clinical experience led to his being accepted at the University of Pittsburgh into their Multi-organ Transplant Fellowship Program (now known as the Thomas E. Starzl Transplant Institute) under the tutelage of Dr. John Fung.

Dr. Lim aspired to add to his extensive transplant training by going to the University of Chicago, to obtain greater pediatric liver transplant experience, and, while there, was able to train under the likes of Drs. Richard Thistlethwaite, Jim Piper, E. Steve Woodle, Mike Millis, and David Cronin. This extensive training served him well with his first job at the University of Maryland, where, during his time, they had the second largest pancreas transplant program in the country. In addition, Dr. Lim helped grow the country's largest laparoscopic donor nephrectomy program while at the University of Maryland. He was recruited by Dr. Jim Piper to become the Director of Pancreas Transplant at Westchester Medical Center and he developed that program to be the largest solitary pancreas program at the time in New York. His successful pancreas transplant experience led to his being recruited to the University of Medicine and Dentistry of New Jersey (UMDNJ) at New Brunswick (now Rutgers University) as the Director of their Pancreas Program as well as the Co-director of the Living Donor Program. During his tenure, he helped the transplant program grow to be the second largest in the state of New Jersey.

Dr. Lim's multi-organ experience allowed him to join his mentor, Francisco Badosa, as the Chief of Kidney and Living Donor Transplant at Lankenau Medical Center. The expertise with growing a transplant program led to his being recruited to Hackensack University Medical Center (HUMC) as their Chief of Transplant. HUMC was searching for a candidate to lead their program which became inactive and unable to perform transplants due to

their difficulties with quality and patient safety. Led by Dr. Lim, extensive improvements to quality, regulations, and, most of all, patient safety were made, and they successfully reactivated their program.

Dr. Lim moved with his wife, Carolyn, and their two daughters, and most recently joined the transplant program in Denver at Porter Adventist Hospital and is hoping to continue to make positive improvements to their program as well.

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Surgical Technique of Pancreas Transplantation

Muhammad Arsalan Khan, Fowler R. Smith, and Jeffrey Rogers

Contents

Abstract

Pancreas transplantation has become accepted as the only definitive long-term treatment that reliably restores euglycemia by restoring endogenous insulin production and improving glucose counterregulation in patients with type 1 diabetes mellitus and in carefully selected patients with insulin-dependent type 2 diabetes mellitus. Despite five decades of experience and with more than 41,000 pancreas transplants performed worldwide through 2011, a multitude of variations exist in operative technique, reflecting the lack of consensus regarding the best method for implanting a pancreas allograft into a recipient. These differences in technique are primarily related to the method of pancreatic exocrine secretion drainage and the site of portal-venous drainage. The surgical technique of pancreas transplantation has evolved over time in response to technical complications and physiologic derangements associated with earlier

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methods of implantation. This chapter reviews the historical development of the pancreas transplant technique and elaborates on the rationale for the different variations currently practiced. Detailed descriptions of the most common technical approaches to implantation are provided.

Keywords
Pancreas transplantation · Technique · Systemic-enteric drainage · Systemic-bladder drainage · Portal-enteric drainage

Introduction

Pancreas transplantation is widely accepted as the only definitive long-term treatment that reliably restores euglycemia by restoring endogenous insulin production and improving glucose counterregulation in patients with type 1 diabetes mellitus and in carefully selected patients with insulin-dependent type 2 diabetes mellitus. The procedure renders patients insulin-free without the risk of severe hypoglycemia; improves quality of life and life expectancy; and can prevent, stabilize, and potentially reverse chronic complications of diabetes (Gruessner and Gruessner 2013). Pancreas transplantation is most commonly performed in conjunction with kidney transplantation in patients with advanced diabetic nephropathy (simultaneous kidney-pancreas transplant, SPK) but may also be performed in patients following successful deceased donor or living donor kidney transplantation (pancreas after kidney transplant, PAK). Much less commonly, pancreas transplantation is performed in nonuremic type 1 diabetics with glucose hyperlability, failure of exogenous insulin therapy, frequent episodes of life-threatening asymptomatic hypoglycemia, and well-defined secondary complications of diabetes that might benefit from improved glycemic control (pancreas transplant alone, PTA). PAK and PTA are collectively referred to as solitary pancreas transplants. In all cases, the benefits of pancreas transplantation come at the expense of major intra-abdominal surgery and the need for chronic immunosuppression. For recipients of primary deceased donor pancreas transplants, 1-year pancreas graft survival (insulin-free) rates are 85% in SPK, 80% in PAK, and 78% in PTA, with pancreas graft half-lives of nearly 14 years in SPK and 10 years in solitary pancreas transplant recipients (Gruessner 2011; Israni et al. 2012; Opelz 2013).

Despite five decades of experience and with more than 41,000 pancreas transplants performed worldwide through 2011, as documented in the International Pancreas Transplantation Registry (IPTR) 2013 report, a multitude of variations exist in operative technique, reflecting the paucity of evidence and the resultant dearth of consensus regarding the best method for implanting a pancreas allograft into a recipient. These differences in technique are primarily related to the method of pancreatic exocrine secretion drainage and the site of portal-venous drainage. Whether the pancreas is transplanted as a solitary organ or in combination with a kidney and whether the recipient has undergone previous kidney and/or pancreas transplantation also represent variations that may result in different operative approaches.

The surgical technique of pancreas transplantation has evolved over time in response to technical complications and physiologic derangements associated with earlier methods of implantation. Ongoing surgical innovation and creativity have aimed to optimize functional outcomes and recreate normal anatomy and physiology. Consequently, the most common techniques of pancreas transplantation that are currently employed are best understood in terms of how they came to be developed from a historical perspective. This chapter will review the historical development of pancreas transplantation technique and will discuss the rationale for the development and implementation of the various technical approaches. Detailed descriptions of the most common methods of implantation currently practiced will be provided.

History of Pancreas Transplantation and Evolution of Surgical Technique

On December 17, 1966, William Kelly and Richard Lillehei performed the first successful human pancreas transplant at the University of Minnesota (Kelly et al. 1967). A twenty-eight-year-old

uremic female with type I diabetes received a duct-ligated segmental pancreas graft along with a kidney from a deceased donor. She remained insulin-free for 6 days and this seminal event, in principle, proved the therapeutic power of pancreas transplantation. The ligated duct led to graft pancreatitis and a subsequent pancreatic fistula, and the patient died 2 months after the transplant from sepsis due to surgical complications.

Over the next 5 years, 25 pancreas transplants were performed worldwide at six institutions (Squifflet et al. 2008). Of these, 13 were performed by Lillehei at Minnesota, who changed his technique to transplantation of the whole pancreas along with duodenum, initially with external drainage of pancreatic exocrine secretions through a duodenal stoma and subsequently via duodenojejunostomy. The longest surviving pancreas graft from this series was functioning at 1 year after transplant and defined the criteria of successful pancreas transplantation at the time (Lillehei et al. 1970). The other institutions that contributed to the experience included University of Rio de Janeiro and University of Sao Paulo in Brazil, Buenos Aires Hospital in Argentina, University of Colorado and University of California, Irvine in the USA, and Guy's Hospital in UK. This experience highlights the recurring challenges of early pancreas transplantation related to management of exocrine secretions of transplanted pancreas, rejection leading to early graft failure, and postoperative mortality. Azathioprine-based immunosuppression also resulted in a higher susceptibility of donor duodenal segment to rejection compared to the pancreas or the kidney. This set the stage for next decade and a half, during which segmental pancreas grafts – body and tail, after removal of pancreatic head and attached duodenum – were used almost exclusively for transplantation.

The Era of Segmental Grafts and Contending with the Pancreatic Duct

To facilitate pancreatic exocrine drainage, Marvin Gliedman, at Montefiore Hospital and Medical Center in New York, performed a series of 11 pancreas transplants from late 1971 to the mid-1970s, in which the duct of a segmental pancreatic graft was anastomosed to the native ureter of the recipient after nephrectomy (Gliedman et al. 1973). The longest functioning graft with euglycemia in this series was 50 months. The procedure never achieved widespread acceptance because of problems with leakage from pancreatic cut surface and from the duct-to-ureter anastomosis as well as due to the need for native nephrectomy, which were criticized as negative aspects of this technique.

Another strategy to deal with the duct was developed based on experiments in dogs and pigs, in which the duct of the transplanted pancreas was left open to drain into the peritoneum. The animals tolerated this without any complications, presumably due to the lack of enzymatic activation. In 1976, Mick Bewick, at Guy's Hospital, London, performed the first open-drained pancreas transplant in a human recipient (Bewick 1976). This was followed by a series of 12 cases at University of Minnesota from 1978 to 1980. Three of these pancreas allografts were ultimately removed due to peritonitis or pancreatic ascites. The longest duration of insulin-independence recorded in this series was 18 years, curtailed only by the untimely death of the recipient from an accident.

At about the same time, an alternate technique of pancreatic duct occlusion was developed. Several different teams injected a variety of synthetic materials, such as neoprene, prolamine, and silicone, into the pancreatic duct of a segmental allograft to occlude the duct. Despite numerous complications, including leaks, fistulas and pancreatitis related to duct occlusion, the technique remained popular. Jean-Michel Dubernard, the original proponent of the technique, proposed wrapping the duct occluded pancreatic segment with omentum (omentoplasty) as a way to contain these problems (Dubernard et al. 1979; Dubernard et al. 1987).

A New Beginning: The Era of Cyclosporine, Whole Organ Grafts, and Bladder Drainage of Exocrine Secretions

In 1979, Roy Calne made a landmark contribution to the field of organ transplantation by

demonstrating the clinical utility of cyclosporine for immunosuppression (Calne 2004). Effective immunosuppression opened the door to a new era of transplantation in which graft survival increased dramatically. Simultaneous surgical innovations enabled pancreas transplantation to begin to approach its current level of efficacy. This was followed almost immediately by a worldwide collaboration of the scientific community, with the development of International Pancreas Transplant Registry (IPTR) at the University of Minnesota in 1980 and a series of workshops known as the Spitzingsee meeting in Austria, in 1981, where the pioneers of pancreas transplantation gathered together to review their experiences and brainstorm about potential strategies to improve outcome (Squifflet et al. 2008). Two influential recommendations through the discourse that ensued had a practice-changing effect on operative technique of pancreas implantation over the next 15 years. Hans Sollinger, of University of Wisconsin, proposed draining pancreatic exocrine secretions into bladder as an alternative to enteric drainage to obviate the complications of intestinal anastomotic leaks, abscess, peritonitis, and sepsis associated with enteric drainage. Additionally, there was a consensus that whole organ pancreas graft was a better option than segmental grafts, particularly in an era of more effective immunosuppression.

In 1987, the technique for bladder drainage of whole organ pancreas grafts via duodenocystostomy was described by Dai Nghiem and Robert Corry at the University of Iowa (Nghiem and Corry 1987). This technique was rapidly adopted by most transplant centers in the USA and Europe, and soon thereafter, up to 90% of pancreas transplants were being performed in this way. Bladder drainage could be performed by either anastomosing a duodenal segment to the bladder as originally described (Iowa technique) or by anastomosing a button of duodenum surrounding the pancreatic duct orifice to the bladder (Wisconsin technique). A comparison between bladder drained pancreas transplants with duodenal button versus duodenal segment showed that bladder leaks, pancreatitis, bleeding episodes, and surgically related infections were all decreased with the duodenal segment technique (D'Alessandro et al. 1989); consequently, bladder drainage with duodenal segment became the prevailing technique. Bladder drainage was advantageous because the consequences of anastomotic leak were far less severe than the morbidity associated with enteric leak and could often be managed nonoperatively with Foley catheter decompression of the bladder. Additionally, serial quantitative measurement of urinary amylase could be used to monitor for rejection. Since rejection of the exocrine pancreas precedes rejection of the endocrine pancreas (Gruessner and Gruessner), a decline in urinary amylase could raise concern for rejection and might prompt pancreas biopsy or empiric treatment. Pancreas and kidney rejection occur synchronously approximately 90% of the time in SPK, so the serum creatinine can be used as a surrogate marker for pancreas rejection and can serve as an indication for kidney biopsy or pancreas biopsy, if technically feasible (Gruessner and Gruessner). In solitary pancreas transplantation (PAK and PTA), the absence of a kidney transplant from the same donor makes monitoring for rejection more challenging. Biochemical markers such as serum amylase and lipase can be associated with pancreas rejection but lack sensitivity and specificity. In view of the historically higher incidence of rejection in solitary pancreas transplants compared to SPK transplants, bladder drainage was viewed as the preferred technique for solitary pancreas transplantation and is still favored by some surgeons for these cases. Unfortunately, bladder drainage is associated with a variety of metabolic and urologic complications, including metabolic acidosis due to bicarbonate loss in the urine, dehydration, recurrent urinary tract infections, cystitis, and reflux pancreatitis (Sollinger et al. 1993). These complications were associated with frequent hospital readmissions and the need for enteric conversion in as many as 25% of bladder drained pancreas transplants (Ploeg et al. 1994). Consequently, a shift towards enteric drainage occurred in the mid-1990s. Since 1995, the number of pancreas transplants performed with primary enteric drainage has increased significantly and currently accounts for 91% of SPK, 89% of PAK, and 85% of PTA cases (Gruessner). With contemporary immunosuppression, careful

donor and recipient selection, and surveillance pancreas biopsies in solitary pancreas transplantation, similar long-term pancreas graft survival can be achieved in SPK and solitary pancreas transplant recipients with enteric drainage (Rogers et al. 2014b; Stratta et al. 2014; Bartlett et al. 1996).

The Current Era

Over the last two decades there was prolific growth of pancreas transplantation worldwide, with improvements in graft survival and a decreased incidence of surgical and immunosuppression-related complications; however, in recent years the volume of pancreas transplants performed has begun to decline, presumably due to improvements in diabetes management. The vast majority of deceased donor pancreas transplants are performed as whole organ grafts with variable lengths of duodenum, whereas segmental grafts are rarely obtained from deceased donors but remain the only option for live donor pancreas transplantation (Gruessner et al. 1997; Sutherland et al. 2001). Currently, over 80% of enteric-drained pancreas transplants are performed with systemic venous drainage of the donor portal vein into either the iliac vein or vena cava (Gruessner). This technique is not physiologic because it bypasses the liver and results in systemic hyperinsulinemia. To make pancreas transplantation more physiologic, Osama Gaber and colleagues introduced the technique of portal-venous drainage via the recipient superior mesenteric vein (SMV) in combination with enteric drainage of exocrine secretions (portal-enteric technique) (Gaber et al. 1993). In theory, portal-venous drainage was thought to have potential clinical benefits because it avoids the systemic hyperinsulinemia that occurs with systemic-enteric drainage. Peripheral hyperinsulinemia is known to be associated with dyslipidemia, insulin resistance, and development of atherosclerosis; interestingly, the clinical impact of these adverse events following systemic-enteric drainage has been minimal (Stadler et al. 2010; Katz et al. 1994). It was also hypothesized that portal presentation of donor antigen to the liver after portal-venous pancreas transplantation could be immunologically advantageous and might lower the incidence of rejection compared to systemic venous drainage, and an uncontrolled, retrospective study initially suggested that this might be the case (Philosophe et al. 2001). However, subsequent studies, including a randomized controlled study comparing portal-venous and systemic-venous drainage, failed to show any difference in rejection between the two techniques (Martin et al. 2000; Petruzzo et al. 2000; Stratta et al. 2001). A number of subsequent studies have not shown any differences in metabolic control, specifically, no differences in lipid profile or glycemic control (Bagdade et al. 1996; Petruzzo et al. 2004; Petruzzo et al. 2006). Patient and graft survival also appear to be similar between portal-venous and systemic-venous drainage (Bazerbachi et al. 2012; Martin et al. 2000; Petruzzo et al. 2000; Lo et al. 2001; Stratta et al. 2001). From a technical standpoint, portal-enteric drainage maybe advantageous because it is primarily a mid-abdominal rather than a pelvic procedure, which may be beneficial in patients who have undergone previous kidney and/or pancreas transplants or other pelvic procedures (Rogers et al. 2014). Anastomosis of the donor portal vein to the SMV, which is superficially located in the mesenteric root, also tends to be easier than anastomosis to a deeper iliac vein, especially if the pelvis is narrow. Technical disadvantages of portal-enteric drainage are that the arterial anastomosis may be more difficult, a longer Y-graft is required, and the pancreas graft is often surrounded by bowel, making it more difficult to assess sonographically and more challenging to biopsy percutaneously (Rogers et al. 2014). Currently, portal-enteric drainage accounts for only 18% of SPK and PAK and 10% of PTA transplants with enteric drainage (Gruessner). Although virtually all pancreas transplants are currently performed using technical variations of systemic-enteric, portal-enteric, and systemic-bladder drainage, current thinking dictates that the most appropriate choice of technique is primarily determined by patient anatomy and surgeon experience and preference.

Current Surgical Techniques

Pancreas Anatomy and Bench Reconstruction

Pancreas anatomy and bench reconstruction are detailed in a separate chapter but are summarized herein. The head of the pancreas shares the vascular supply of duodenum, which lies at the interface of embryological foregut and midgut. The superior pancreaticoduodenal artery arises from the gastroduodenal artery (GDA) and represents the foregut arterial supply, whereas the inferior pancreaticoduodenal artery arises from the superior mesenteric artery (SMA) and represents the midgut arterial supply. The splenic artery (SA) courses along the body of pancreas and supplies the body and tail via the dorsal pancreatic artery and multiple segmental branches. Both of these arterial systems are connected through collateral circulation that traverses the head and body of the pancreas. Venous drainage is primarily through the splenic vein (SV) and the superior mesenteric vein (SMV) and via their confluence into the portal vein.

The whole organ vascularized pancreas graft includes an attached duodenal segment along with the entire pancreas. The duodenal segment includes the first, second, and a variable length of third part of duodenum, usually stapled at both the ends and imbricated with a sutured seromuscular layer. The arterial supply includes the donor's SA and SMA, which gives rise to the inferior pancreaticoduodenal artery. Although some surgeons routinely reconstruct GDA to preserve perfusion of the superior pancreaticoduodenal artery, the GDA stump is most commonly ligated, while SA and SMA are reconstructed into a single vessel using a bifurcated donor arterial graft. The type of arterial reconstruction required and the choice of arterial conduit depends primarily on whether systemic or portal-venous drainage is planned. Because the recipient iliac artery is the site of arterial anastomosis in nearly all pancreas transplants, if systemic-venous drainage is to be performed into contiguous iliac veins, a longer arterial conduit is not required. However, if portal-venous drainage is to be performed, graft placement higher along the recipient's SMV in most cases requires a longer arterial conduit that can reach the proximal right common iliac artery. The donor common iliac artery bifurcation into the internal and external iliac arteries is most commonly used for arterial reconstruction. The common carotid artery bifurcation into internal and external carotid arteries can also be used. In the absence of a bifurcated arterial graft from the donor, an end-to-side anastomosis of SA into the SMA can be performed and the distal end of the SMA is used for anastomosis to the recipient artery, although this results in a short common arterial trunk and a more difficult arterial anastomosis in the recipient. When the donor iliac artery is used as the interposition Y-graft, the best size match is usually achieved by anastomosing the external iliac artery to the SMA and the internal iliac artery to the SA. This works best when systemic venous drainage is to be performed since a long arterial conduit is not required. However, with portal-venous drainage, a long Y-graft is required and the best way to maximize arterial length is to anastomose the longer limb of the external iliac artery to the shorter SA and the shorter limb of the internal iliac artery to the longer SMA. On occasion, an extension graft (of distal external iliac artery or other donor arterial graft) may be anastomosed end-to-end to the common iliac artery conduit in order to further lengthen the arterial reconstruction. The donor portal vein is dissected circumferentially and is the outflow vein which is anastomosed to the iliac vein, vena cava, or SMV of the recipient. The SA and SV are doubly ligated at the tail of the pancreas, the short gastric vessels are ligated, and the spleen is removed. The stumps of the SMV and SMA in the root of the small bowel mesentery are typically stapled with a vascular stapler. Many surgeons prefer to reinforce this staple line with running nonabsorbable suture to prevent bleeding after reperfusion of the graft.

Intraoperative Preparation and Incision

Most pancreas transplants are performed through a midline laparotomy incision, in large measure, because this approach is associated with fewest wound complications and allows simultaneous

placement of a kidney allograft when required. Moreover, it preserves all options for vascular reconstruction and exocrine drainage. An additional advantage of intraperitoneal placement of the pancreas is that it allows internal absorption of peripancreatic collections through the peritoneal lymphatic circulation. Alternatively, a transverse abdominal incision can be used for intraperitoneal graft placement. Some surgeons prefer retroperitoneal placement of the pancreas into the iliac fossa via a J-shaped iliac incision. A potential advantage of pelvic retroperitoneal placement is that this location is easily approached for pancreas biopsy. In such cases, the peritoneum is accessed via a peritoneal window for enteric drainage of exocrine secretions and for intraperitoneal drainage of peripancreatic fluid collections.

After induction of general anesthesia, a central venous catheter and radial arterial line are placed for monitoring. A Foley catheter is placed and a nasogastric tube is inserted according to surgeon preference. Pancreas transplantation using enteric drainage without insertion of a nasogastric tube has been described and can be performed with good results (Barth et al. 2008). Typically a first-generation cephalosporin is used for surgical-site prophylaxis, with doses repeated every three hours intraoperatively and two additional doses administered at eight hour intervals postoperatively. Following an initial time-out and incision, a formal abdominal exploration is performed, and the nasogastric tube is properly positioned in the gastric antrum. A Bookwalter or other self-retaining retractor is used for exposure.

Systemic-Enteric and Systemic-Bladder Drainage

The pancreas is typically placed on the right side due to easier access to the iliac vein or vena cava for venous anastomosis. The right colon, cecum, and terminal ileum are mobilized medially along the peritoneal reflection to facilitate exposure of the iliac vessels in the right iliac fossa. The right common iliac artery is dissected circumferentially to the level of the aortic bifurcation. The external iliac artery is also mobilized circumferentially. Although the arterial dissection is intraperitoneal, ligation of large lymphatics is recommended. The native ureter and gonadal vein are retracted laterally and protected. The distal vena cava is exposed and the external iliac veins are mobilized circumferentially. Many surgeons prefer to ligate and divide the internal iliac vein in order to maximize anterior mobilization of the common and external iliac vein. This facilitates anastomosis of a short donor portal vein and also minimizes the likelihood of tension on the portal vein. The internal iliac vein is best divided between silk ties with each end suture ligated with polypropylene suture to prevent bleeding. The pancreas can be oriented either head down (Fig. 1) or head up (Fig. 2) for systemic-enteric drainage according to surgeon preference but only head down for systemic-bladder drainage. Most patients have iliac artery atherosclerosis and calcifications, the location and extent of which often dictate the site of arterial anastomosis. Consequently, the site of venous anastomosis is typically limited by the location of the arterial anastomosis. The common or external iliac arteries can be used for the arterial anastomosis. The venous anastomosis can be performed on the vena cava, the common iliac vein, or external iliac veins. When the pancreas

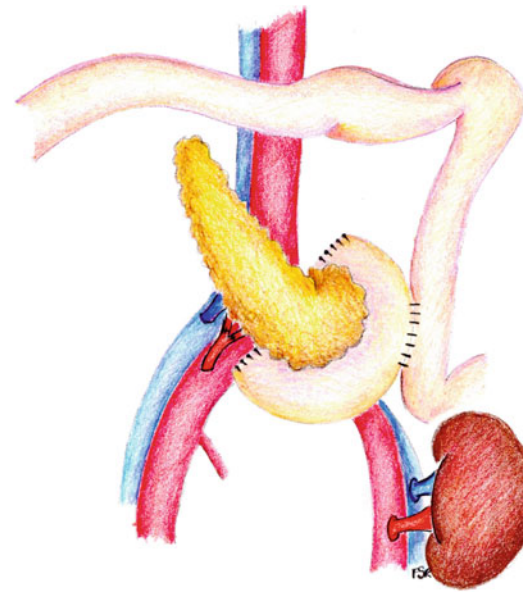

Fig. 1 Systemic-enteric drainage

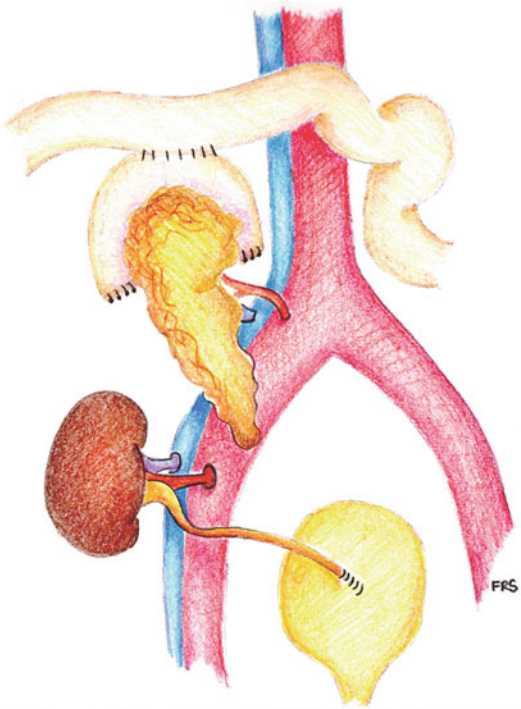

Fig. 2 Systemic-enteric drainage (pancreas head up) with ipsilateral kidney transplant

is positioned head down, it is important to not perform the arterial and venous anastomoses too distally on the external iliac vessels, especially in a narrow pelvis, as this can increase tension on both the portal vein and the transplant duodenum due to compression against the pelvic brim. The pancreas is placed in a laparotomy pad containing ice slush, and the Y-graft and portal vein are brought out through a hole cut in the laparotomy pad. The portal vein and Y-graft are carefully positioned to prevent scissoring when the vascular anastomoses are performed. Prior to clamping the vein, heparin 2000–3000 units (30–50 mg/kg) is administered intravenously in patients with a known thrombophilia and in recipients of a solitary pancreas transplant, since these patients may be more prone to graft vascular thrombosis. The vein is controlled with a large side-biting vascular clamp and a venotomy is created corresponding to the diameter of the donor portal vein. The venotomy is irrigated with heparinized saline solution. The portal vein may be extended with a segment of donor iliac vein if additional donor vein length is required; however, this is best avoided unless absolutely necessary since there is some evidence that a portal vein extension graft may increase the risk of venous thrombosis (Troppmann et al. 1995). The portal vein is anastomosed end-to-side to the recipient vein with 5–0 or 6–0 polypropylene suture using standard vascular technique. After completion of the venous anastomosis, a bulldog clamp is placed on the portal vein just above the anastomosis and the side-biting clamp is released, restoring iliac venous return from the right lower extremity. Any areas of venous anastomotic bleeding are repaired with polypropylene suture. The recipient iliac artery is then controlled with either a side-biting vascular clamp or with separate proximal and distal vascular clamps. An arteriotomy is made in the previously selected part of the iliac artery and is widened with a 4.8 mm or 5.2 mm arterial punch to facilitate anastomosis to the end of the Y-graft. The arteriotomy is irrigated with heparinized saline solution. The Y-graft is shortened as much as possible to prevent redundancy and kinking but must be left long enough to avoid tension. Prior to arterial anastomosis, the Y-graft is properly oriented with respect to the portal vein to prevent twisting or scissoring. The Y-graft is then anastomosed end-to-side the recipient artery. Mannitol 12.5 g is typically administered intravenously before reperfusion to minimize reperfusion pancreatitis. The laparotomy pad ice wrap is then removed and the pancreas is reperfused by first releasing the venous clamp followed by the arterial clamp. Hemostasis is achieved with gauze compression, electrocautery, and suture ligatures as needed. Common areas of bleeding after reperfusion are at the base of the portal vein and SMA, the small bowel mesentery staple or suture line, and at the distal SA and SV. After hemostasis is confirmed, attention is turned towards drainage of the exocrine secretions. When systemic-enteric drainage is performed, a segment of mid-jejunum is selected for duodenoenterostomy. Some surgeons emphasize the importance of not performing the bowel anastomosis too distally in the small bowel to avoid an increased risk of diarrhea; however, since the majority of water absorption occurs in the colon, this is more of a

theoretical concern. More importantly, the segment of recipient small bowel selected for the site of duodenoenterostomy should avoid tension on the donor duodenum and portal vein, especially when the pancreas is oriented head down. This is critical to minimize the likelihood of enteric leak and venous thrombosis, respectively. When the pancreas is oriented head up, a segment of proximal jejunum is usually selected for duodenoenterostomy. Prior to bowel anastomosis, the recipient bowel is controlled proximally and distally with bowel clamps to minimize enteric spillage. It is important to make sure that the pancreas is oriented properly with the mesentery facing upwards to avoid twisting of the portal vein and Y-graft. The authors prefer a 2-layer hand sewn, side-to-side anastomosis. The inner layer is performed with running, interlocking 3–0 polydioxanone for optimal hemostasis and the outer seromuscular layer is performed with 3–0 silk interrupted Lembert sutures. Alternatively, bowel anastomosis with a linear (Lam et al. 2006) or circular (Fridell et al. 2004a) stapler is favored by some surgeons. A Roux-en-Y diversion is preferred by some surgeons but is usually not necessary unless there are concerns about whether the transplant duodenum is adequately perfused. Bladder drainage of exocrine secretions can also be performed if there is any concern about the viability of the donor duodenum since the morbidity of a bladder leak is significantly less than an enteric leak. In cases of SPK, the kidney can be implanted on the left iliac vessels. Alternatively, the kidney can be implanted on the right external iliac artery and vein distal to the pancreas (Fridell et al. 2004b). This technique shortens the vascular dissection by avoiding the need to mobilize the sigmoid colon and expose the left iliac vessels. An additional benefit of ipsilateral kidney graft implantation is that it preserves the left iliac vessels for future transplantation. Ipsilateral kidney graft implantation should only be performed in cases of "head up" systemic-enteric pancreas transplantation or portal-enteric drainage (in which the pancreas and kidney are separated by the small bowel mesentery) to avoid the risk of having the duodenoenterostomy directly overlying the kidney graft vascular anastomoses.

If systemic-bladder drainage is performed (Fig. 3), the pancreas must be implanted on the iliac vessels such that the donor duodenum easily reaches the bladder without tension. Adequate bladder capacity is also a prerequisite. The bladder is distended with antibiotic irrigation solution via a three-way Foley catheter and the down drain is clamped. An area on the bladder dome is selected and the overlying peritoneal layer is opened with electrocautery. A posterior seromuscular layer of interrupted 3–0 silk suture is placed to approximate the bladder and transplant duodenum. These sutures must not be full thickness through the bladder to prevent leak and stone formation. The bladder is opened with the electrocautery and a corresponding opening is made in the transplant duodenum. The inner layer is performed with full thickness running 3–0 polydiaxonone suture and then the anterior seromuscular layer is completed with interrupted 3–0 silk Lembert sutures. The authors prefer to place a closed suction drain around the vascular anastomoses and under the bowel or bladder anastomosis, but this is optional. The pancreas is positioned in the right paracolic gutter and the right

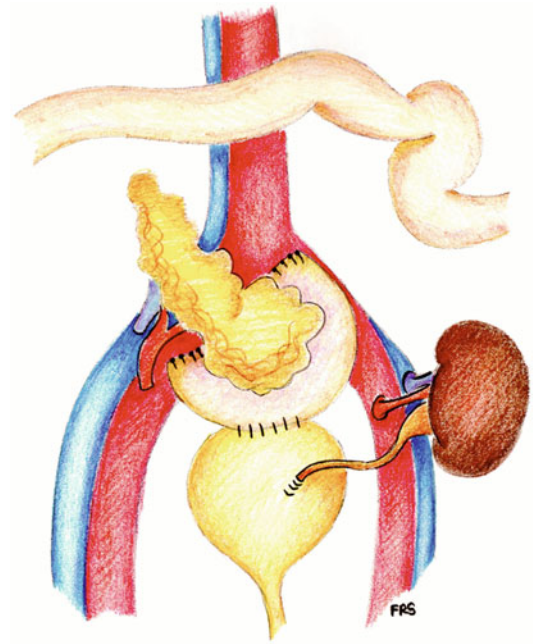

Fig. 3 Systemic-bladder drainage

colon is replaced over the pancreas. If an ipsilateral kidney transplant is performed, the right colon is tacked to the anterolateral abdominal wall overlying the kidney to prevent medial rotation and vascular torsion of the kidney.

Portal-Enteric Drainage

Abdominal exploration and circumferential exposure of the right common iliac artery to the level of the aortic bifurcation are performed as described above for systemic-enteric drainage. The external iliac artery and vein can also be exposed as described above if ipsilateral placement of a kidney graft is planned. The transverse mesocolon is retracted cephalad and the remaining viscera are retracted caudad to expose the root of the small bowel mesentery. The SMV can usually be identified in the mesentery between the duodenum and the palpable SMA. If the mesentery is thickened and the SMV is not visible, the SMA can be identified with a Doppler probe and the SMV can usually be found just to the right of the SMA. The mesentery is divided longitudinally over the SMV with the electrocautery and a 3–4 cm length of vein is exposed. Large side branches are encircled with vessel loops. If the vein diameter is >6 mm, then no further dissection is required. However, if the vein size is inadequate, a larger segment of vein can usually be exposed by carrying the mesenteric dissection higher. Portal-enteric drainage is not advisable if the SMV is <6 mm or if it is too deep or difficult to access, as is often the case in recipients with a BMI >30 kg/m^2 (Rogers et al. 2014a). It is common for the SMV to develop vasospasm in the process of dissection, so it is important to assess the SMV diameter before this occurs. Topical papaverine can be used to alleviate vasospasm of the SMV. Portal-enteric drainage is also contraindicated if the Y-graft is not long enough to traverse the small bowel mesentery and easily reach a segment of noncalcified iliac artery that is suitable for arterial anastomoses. In such cases, portal-enteric drainage is abandoned and the pancreas is typically implanted with systemic-enteric drainage. Circumferential dissection of the SMV is not required as long as the SMV can be safely controlled with a small side-biting clamp. Once the SMV dissection is completed and a landing zone on the iliac artery suitable for vascular anastomosis is identified, a small window is created in an avascular area of the distal ileal mesentery just above the iliac artery for passage of the Y-graft. Care must be taken not to injure vessels, bowel, or native duodenum when creating this window. Alternatively, a large mesenteric window can be created in the ileal mesentery allowing completion of both arterial and venous anastomoses anterior to the mesentery. This large mesenteric window must be partially closed after revascularization to prevent internal herniation of bowel. Yet another approach is to anastomose a segment of donor iliac or carotid artery, if available, to the recipient proximal common iliac artery prior to implantation of the pancreas. This jump graft is tunneled retrograde through the window in the ileal mesentery so that it is visible on the anterior side of the mesentery and available for end-to-end anastomosis to the Y-graft. The pancreas is placed in a laparotomy pad containing ice slush. The Y-graft is marked anteriorly to maintain orientation when it is passed through an opening cut in the laparotomy pad and when it traverses the mesenteric window. The pancreas is position head up with the mesenteric root anterior. If indicated, heparin is administered intravenously as described above. The SMV is controlled with a small side-biting vascular clamp, and a venotomy corresponding to the diameter of the donor portal vein is created. The venotomy is irrigated with heparinized saline solution. The portal vein is anastomosed end-to-side to the recipient vein with 6–0 polypropylene suture using standard vascular technique. Using a small needle (BV-1) is advisable to minimize tearing of the SMV, which can be quite thin walled. After completion of the venous anastomosis, a bulldog clamp is placed on the portal vein just above the anastomosis and the side-biting clamp is released, restoring portal venous return from the small bowel and testing the venous suture line for hemostasis. The Y-graft is then passed through the mesenteric window so that it emerges above the previously exposed common iliac artery,

taking care to ensure that the arterial conduit is not twisted as it traverses the mesentery. The Y-graft is trimmed to an appropriate length, and the distal end is beveled to enlarge the size of the anastomosis. With retractors pulling cephalad on the distal ileum and cecum, the end of the Y-graft should just reach the site of arterial anastomosis without tension since some additional redundancy is achieved when the retractors are released. If too much slack is left in the Y-graft prior to arterial anastomosis, there may be enough redundancy to result in kinking of the arterial conduit after the retractors are released. The proximal common iliac artery is controlled with a large side-biting vascular clamp or with individual clamps on the proximal common iliac, external iliac, and internal iliac arteries. An arteriotomy is made and widened with a 4.8 mm or 5.2 mm aortic punch, and the Y-graft is anastomosed end-to-side to the iliac artery with 5–0 polypropylene running suture using standard vascular technique. Before reperfusion, mannitol 12.5 g is administered intravenously. A vascular clamp is then placed on the Y-graft proximal to the arterial anastomosis and the iliac artery clamps are released. This allows the arterial anastomosis to be tested before reperfusing the pancreas and for any necessary additional sutures to be placed at the arterial anastomosis to secure hemostasis. This also allows the surgeon to focus all attention on achieving hemostasis of the pancreas graft above the mesentery after reperfusion. The laparotomy pad ice wrap is then removed and the pancreas is reperfused by first removing the bulldog clamp from the portal vein followed by removing the clamp from the Y-graft. Hemostasis is then achieved as described for systemic-enteric drainage. The authors prefer to perform a duodenoenterostomy between the posterior aspect of the distal transplant duodenum and a segment of ileum approximately 5 ft from the ileocecal valve. This allows for dependent drainage from the atonic transplant duodenum into the recipient bowel (Fig. 4). The bowel anastomosis is performed as a side-to-side two-layer hand sewn anastomosis as described for systemic-enteric drainage, although the enteric anastomosis can also be performed with staplers according to surgeon preference. Some surgeons prefer to anastomose the transplant duodenum into a defunctionalized Roux-en-Y limb with or without a venting jejunostomy (Zibari et al. 2000), into an omega loop (Losanoff et al. 2006), or directly into the native duodenum or stomach (Shokouh-Amiri and Zibari 2011; De Roover et al. 2007; Hummel et al. 2008). The

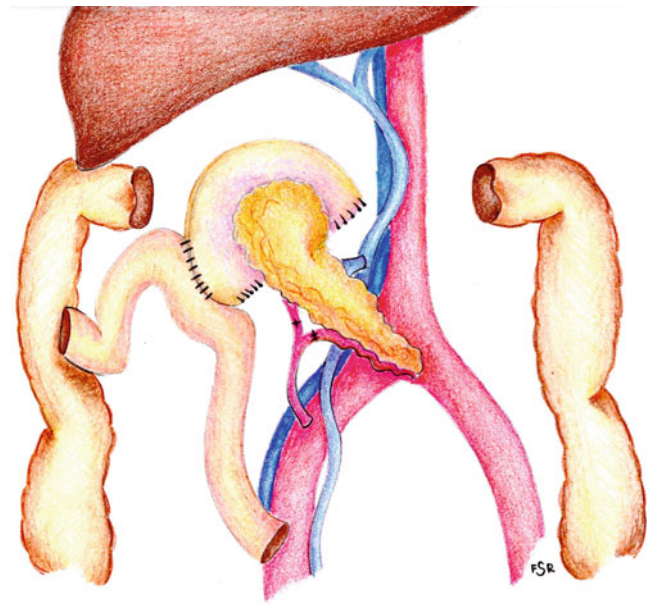

Fig. 4 Portal-enteric drainage

latter three options are uncommon and have been reported in some recent small series; these procedures have the advantage of allowing easy access for endoscopic surveillance and biopsy of the transplant duodenum and pancreatic head but may be associated with greater morbidity if there is an anastomotic leak. Although it involves creating an additional enteric anastomosis, a diverting Roux-en-Y limb is usually the safest procedure if there is any question about whether the transplant duodenum is adequately perfused.

A newer variation of portal-enteric drainage, described by Ugo Boggi, involves retroperitoneal placement of the pancreas with vascular anastomosis to the lateral aspect of the SMV and the proximal common iliac artery (Boggi et al. 2005). A Roux-en-Y limb is brought through a window in the right colon mesentery for side-to-side enteric anastomosis. Alternatively, a side-to-side duodenoduodenostomy can be performed to the native duodenum, which eliminates the need for a Roux limb or mesenteric window. Regardless of technique, it is important to ensure that the efferent limb of small bowel beyond the duodenoenterosomy is not kinked, since this can result in bowel obstruction and duodenal blowout. Prior to abdominal closure, the authors prefer to place a closed suction drain around the pancreatic vessels and beneath the bowel anastomosis, although this is optional.

Conclusion

Since the first pancreas transplant was performed in 1966, the technical evolution and ongoing refinements of the procedure, combined with improvements in organ recovery and preservation, major advances in immunosuppression and anti-infective prophylaxis, and increased experience with donor and recipient section, have resulted in excellent long-term patient and graft survival. Although a variety of implantation techniques are currently practiced, there are advantages and disadvantages associated with each approach. Familiarity and experience with the various surgical options currently available provide pancreas transplant surgeons with the flexibility to choose the best operative approach for a specific set of donor and recipient characteristics, thereby maximizing the likelihood of a technically and functionally successful pancreas transplant.

Cross-References

▶ Donor Evaluation and Procurement
▶ Surgical Complications of Pancreas Transplant

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Autologous Islet Cell Transplant

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Abstract

Transplantation of islets isolated from autologous pancreas, commonly called *islet autotransplantation* (IAT), has been developed primarily for the treatment of refractory chronic pancreatitis (CP). CP is an irreversible and progressive inflammatory disease of the pancreas in which the patients often experience severe abdominal pain and malnutrition. Diabetes can result in advanced stage CP if the inflammatory response damages pancreatic islets. Multiple causes such as genetic mutations, alcohol abuse, autoimmunity, recurrent acute pancreatitis, and obstruction of the pancreatic duct are involved in the development of CP. Medication and endoscopic procedure are available for CP treatment; however, a significant portion of CP patients are eventually referred to a surgical clinic. Surgical resection of the inflamed pancreas is a treatment option if CP patients do not respond to other means of treatment although there is loss of pancreatic exocrine and endocrine functions after even a partial resection of an inflamed pancreas. IAT following total pancreatectomy (TPIAT) allows elimination of severe abdominal pain while preserving pancreatic endocrine function in a single operation. TPIAT has been applied for the treatment of benign pancreatic tumors in addition to CP. Due to the remarkable improvements in islet isolation methodologies and surgical procedures, there is a significant increase in the number of transplants and improved graft outcomes. Future directions of TPIAT include changes to current patient selection criteria and enhancing islet graft function by inhibition of the peritransplant inflammatory reaction.

Keywords

Chronic pancreatitis · Pancreatic islet isolation · Islet infusion · Inflammatory response

Introduction

Chronic pancreatitis (CP) is an irreversible inflammatory disease that develops pancreatic exocrine insufficiency and, later on, leads to the failure of the endocrine tissue in the Islets of Langerhans (Braganza et al. 2011; Etemad and Whitcomb 2001). The total number of hospitalizations due to CP in the USA has been reported to be more than 56,000 annually, which resulted in a sum of over $600 million per year for medical costs (Everhart and Ruhl 2009). Surgical procedures are considered when medication and/or endoscopic therapy have failed. Total pancreatectomy (TP) for severe CP was first successfully performed in November, 1944. However, the patient was found dead in her home due to severe hypoglycemia ten weeks after TP (Waugh et al. 1946; Whipple 1946). As such, a major risk of pancreatic removal is surgical diabetes, which causes severe hypo- and hyperglycemia (Matsumoto 2011). David Sutherland first performed TPIAT at the University of Minnesota in 1977 to reduce the risk of surgical diabetes and to eliminate severe abdominal pain (Najarian et al. 1979). A total of 525 recipients of autologous islets have been registered in the Collaborative Islet Transplant Registry (CITR), the international registry for pancreatic islet transplantation (Coordinating Center 2014). At present, the largest series of TPIAT in the world has been reported from the University of Minnesota (over 450 recipients) (Sutherland et al. 2012). Other major US centers performing TPIAT include the University of Cincinnati, Medical University of South Carolina, the University of Alabama, and the Cleveland Clinic. Baylor University Medical Center has performed more than 100 cases since it initiated a TPIAT program in 2006.

Etiology of Chronic Pancreatitis

Chronic pancreatitis (CP) is defined as a progressive inflammatory disease caused by one or multiple factors (Conwell et al. 2014; Etemad and Whitcomb 2001). Well-known risk factors of CP include heavy alcohol consumption and smoking (Muniraj et al. 2014). The M-ANNHEIM classification, a clinical classification system of CP, identifies alcohol consumption, nicotine consumption, nutritional factors of high fat and protein, hereditary factors, efferent duct factors, autoimmunity, and rare metabolic diseases as risk factors (Schneider et al. 2007). According to the North American Pancreatitis Study 2 (NAPS2), a multicenter trial for CP procedures conducted between 2000 and 2006 where 539 patients were enrolled, 44.5% of the CP cases were determined to be alcoholic CP (Cote et al. 2011). The alcoholic CP cohort of the NSAP2 study consisted of 28.6% of idiopathic, 8.7% of genetic, 2.2% of autoimmune, 8.7% of obstructive, and 7.2% of the other causes (Cote et al. 2011). This proportion of alcoholic CP, however, was less than previous reports and the authors' estimation. A clinical study at Mayo Clinic from 1976 to 1982 reported that the proportions with any alcohol consumption and heavy alcohol consumption in CP patients were 84% and 58%, respectively (Layer et al. 1994). Smoking is also considered an independent risk factor of CP. Smokers were 7.8–17.3 times as likely as nonsmokers to develop CP, and this ratio was directly proportional to the amount of smoking (Lin et al. 2000; Talamini et al. 1999). Another major risk factor of CP is abnormal findings in the pancreatic duct: pancreas divisum, annular pancreas, pancreatic duct stenosis/obstruction, and sphincter of Oddi dysfunction. According to the classical understanding of CP development, excessive pancreatic enzyme activity, autolysis, and repeated inflammation are involved in the development of CP although the detailed mechanism of CP is still unknown (Witt et al. 2007). The symptoms of CP such as malnutrition and diabetes are seen in the advanced phase of the disease.

Regarding hereditary pancreatitis, Whitcomb and colleague identified a mutation in the cationic trypsinogen gene (Protease, serine, 1; PRSS1) as a cause of hereditary pancreatitis in 1996 (Whitcomb et al. 1996). Subsequently, other mutations of PRSS1 and mutations in SPINK1, CTRC, CFTR, and CPA1 have been reported to be associated with CP development (Cohn et al. 1998; Sharer et al. 1998; Witt et al. 2013; Witt et al. 2000; Witt et al. 2006). More recently, hereditary chronic pancreatitis has been considered as a disease caused by complex multiple gene mutations that regulate pancreatic enzyme activity (Masamune 2014). PRSS1 and SPINK1 have been demonstrated to increase trypsin activity. PRSS1 is a cationic trypsinogen gene. Mutation variants including p.R122H and p.N291 in PRSS1 are associated with CP onset (Masamune 2014; Whitcomb et al. 1996). SPINK1 is pancreatic secretary inhibitor, and Witt et al. reported that 22 out of 96 juvenile CP patients had PRSS1 mutations including p.N34S and c.194+2 T>C (Witt et al. 2000). Chymotrypsin C (CTRC) degrades all human trypsin trypsinogen isoforms with high specificity (Rosendahl et al. 2008; Szmola and Sahin-Toth 2007). The loss of CTRC activity, therefore, would impair the protective trypsinogen- and trypsin-degrading activity of CTRC (Zhou and Sahin-Toth 2011). Rosendahl et al. found two alterations (p.R254W and p.K247_R254del) that were significantly overrepresented in pancreatitis patients (Rosendahl et al. 2008). Regarding CPA1 (carboxypeptidase A1), Witt et al. showed that functionally defective CPA1 variants are associated with pancreatitis, especially early onset pancreatitis (Witt et al. 2013).

Autoimmune pancreatitis (AIP) is classified histologically as type 1 and type 2 according to the International Consensus Diagnostic Criteria (ICDC) presented in 2011 (Kawa et al. 2014; Shimosegawa et al. 2011). Histologically, type 1 AIP is characterized by lymphoplasmacytic sclerosing pancreatitis (LPSP). Type 2 AIP is characterized by idiopathic duct-centric pancreatitis (IDCP) with granulocytic epithelial lesions (GEL). Type 1 AIP is now considered as a

component of multisystemic IgG4 disease. A cohort study in the UK showed that serum IgG4 was elevated (>1.4 ng/l) by up to 70% above normal at diagnosis and up to 77% above normal during follow-up (Huggett et al. 2014).

Pancreatic divisum and sphincter of Oddi disorders are risk factors that can induce congestion of pancreatic enzymes and increase pancreatic exocrine enzyme activity due to mixing of fluids from the bile duct into pancreas (Tarnasky et al. 1997). After differential diagnosis, these patients will be classified etiologically using the TIGAR-O criteria, which also suggest potential treatment options (Etemad and Whitcomb 2001; Huggett et al. 2014).

Diagnosis of CP

CP can be diagnosed by present clinical symptoms, medical history, family history, laboratory data, and image analysis such as transabdominal ultrasonography (US), computed tomography (CT), and magnetic resonance imaging (MRI), although no CP-specific reliable biomarker has been established. CP patients commonly show severe abdominal pain (such as upper abdominal pain) or back pain, which may be exacerbated by intake of a high-fat diet or alcohol. Patients often lose their appetite and body weight can drop, leading to malnutrition because of nausea, vomiting, and/or diarrhea. In the laboratory data, the activity of pancreatic enzymes such as amylase or elastase increases with the onset of symptoms and correlates with an increase in the number of white blood cells (WBC) and a higher level of C-reactive protein (CRP).

The transabdominal US, CT, and MRI are noninvasive clinical imaging procedures to confirm CP. However, these studies are not sensitive enough to diagnose the early stages of CP (Rosendahl et al. 2007). The pancreas with advanced stage CP demonstrates morphological changes including atrophy, calcification, and dilation of the pancreatic duct. According to a study by a group from the Mayo Clinic in 1989, atrophy and calcification of the pancreas and duct dilation were seen in 54%, 50%, and 68% of CP patients, respectively. MRI is more sensitive for diagnosing CP, and ductal abnormalities are specific and reliable signs of CP in MRI scans (Conwell et al. 2014; Luetmer et al. 1989).

Further evaluations such as endoscopic ultrasound (EUS) or endoscopic retrograde pancreatogram (ERP) are used once CP is highly suspected. EUS allows changes in the pancreatic parenchyma and pancreatic duct to be verified by placing a US probe in the stomach or duodenum. EUS criteria are based on ductal and parenchymal findings described by the International Working Group using minimum standard terminology (Catalano et al. 1998; Wallace et al. 2001; Wiersema and Wiersema 1995). ERP is not frequently used for diagnostic purposes because of its invasiveness (Conwell et al. 2014). ERP, however, is a sensitive procedure to detect small changes in the pancreatic duct, such as minor stenosis, because it provides a direct visualization of the duct. ERP is applicable for taking a cytological sample and for treating duct stenosis by implanting a stent. The most important concern in TPIAT is to confirm that the pancreatic disease is nonmalignant. Furthermore, ERP is used especially for pancreatic duct stenosis or suspicion of malignant disease to collect cytological or histological biopsies for evaluation. The diagnosis and etiological classification should be comprehensively and carefully done in CP, especially to distinguish CP from oncological disease.

Indication of TPIAT

TP is a radical treatment for CP. The final goal of TP is to attain relief from intractable pain. IAT is the replacement of beta cells to prevent surgical diabetes after TP. Thus, the final goal of TPIAT is to alleviate pain due to CP while retaining pancreatic endocrine function (Chinnakotla et al. 2014). Retaining any amount of pancreatic endocrine function greatly eliminates the occurrence of severe hypoglycemic episodes due to the complete absence of functional islets.

TPIAT is performed for carefully selected CP patients after failure of treatment with medication or endoscopic procedures. Indications of TPIAT are

Table 1 Inclusion and exclusion criteria for TPIAT at Baylor University Medical Center

Inclusion criteria	1. Diagnosed with chronic pancreatitis by a treating gastroenterologist or pancreatologist or other indications as jointly agreed upon by islet transplant surgeon and pancreatologist 2. Prior procedures (celiac block or pancreatic duct stents) that have failed or only provided temporary pain relief 3. Narcotic dependence for chronic pain due to pancreatitis 4. Self-reported poor quality of life with use of a formal scale 5. Ability to understand/give informed consent
Exclusion criteria	1. Known or suspected pancreatic malignancy 2. Portal hypertension or significant hepatic fibrosis 3. Cardiac contraindication to major abdominal operation 4. Pulmonary contraindication to major abdominal operation 5. Ongoing nonprescribed substance abuse, including alcohol 6. Profound uncorrected malnutrition 7. C-peptide negative during glucose tolerance test (may be directed for pancreatectomy without autotransplant) 8. Inability to understand/give informed consent

listed in Table 1. Current indications for TPIAT at Baylor University Medical Center include: (i) established diagnosis of CP by a pancreatologist or gastroenterologist, (ii) failure of maximal mediation and/or endoscopic procedures, (iii) severe abdominal pain that has led to narcotic dependence, and (iv) impaired quality of life due to CP. The CP patients who have the following major conditions are not considered for TPIAT: (i) known or suspected pancreatic malignancy, (ii) portal hypertension or significant hepatic fibrosis, (iii) cardiac or pulmonary contraindication to major abdominal operation, (iv) ongoing nonprescribed substance abuse including alcohol, (v) profound uncorrected malnutrition, (vi) C-peptide negative during glucose tolerance, and (vii) inability to understand/give informed consent. Of note, hepatic portal thrombosis is a major adverse event for islet infusion. For this reason, patients who have a risk of portal hypertension are excluded. Recent reports showed that patients with locally limited pancreatic malignancy or benign tumor have undergone TPIAT with successful outcomes (Balzano et al. 2014; Balzano et al. 2013; Yoon et al. 2014). Traumatic pancreatic injury is another indication for TPIAT (Jindal et al. 2010; Thakor et al. 2015).

Total pancreatectomy alone is performed in medical centers that do not have a dedicated facility to isolate functional pancreatic islets. According to previous studies, a large percentage of patients were readmitted for diabetic complications after TP.

Operative Procedure

Major aspects of the TPIAT procedure are shown in Fig. 1. Pancreatectomy is a complicated procedure. Sometimes severe adhesion between the pancreas and surrounding organs is evident, resulting in difficulty in recognizing major vessels connected to the organ. For surgery during pancreatitis attacks, it may be difficult to stop bleeding because of developing capillary vessels. Surgery during the acute phase of pancreatitis should be avoided as much as possible. After laparotomy, whole abdominal assessment is performed to eliminate the possibility of any other oncological disease. The hepatic and splenic flexures are mobilized, and stomach, duodenum, and pancreas head are retracted to the left side. A "wide Kocher maneuver" is performed to separate the head of the pancreas from the inferior vena cava and aorta and to separate the body-tail of the pancreas from the retroperitoneum (Heidt et al. 2007). The gastrocolic and hepatogastric ligaments are widely incised to expose the anterior surface of the pancreas. The third portion of the duodenum is separated from the Treitz ligament as transverse mesocolon. Next, the hepatoduodenal ligament is separated. The common bile duct, proper hepatic artery, and portal vein are identified, and the upper stream of the common bile duct is dissected. In the majority of cases, the gallbladder would have been resected in a previous surgery. The proper hepatic artery and common hepatic artery are divided from the pancreas. The gastroduodenal artery and the root of

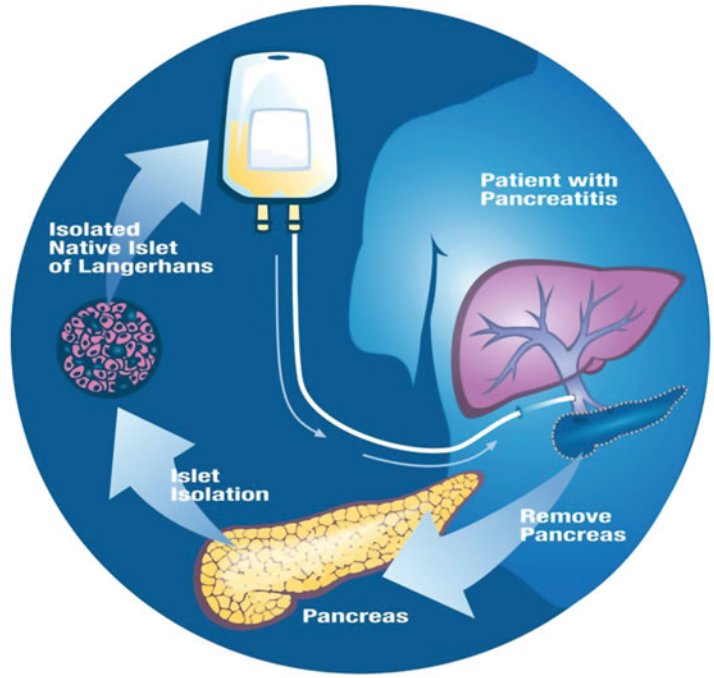

Fig. 1 Schematic representation of the TPIAT procedure for patients with chronic pancreatitis

the splenic artery are taped to preserve blood flow into the pancreas as long as possible, and the right gastric artery is cut. The distal side of end of gastroduodenal artery is cut after dissecting the right epigastric artery. Then, the transverse colon is retracted to the upper side, and the mesocolon and duodenum are separated. The jejunum is pulled to the right side after being cut with a linear stapler and retracting down the transverse colon. After that, the mesentery of the jejunum is cut, the uncus of the pancreas is separated from the superior mesenteric artery, and the inferior pancreaticoduodenal artery is cut. After separating the pancreas and portal vein, the splenic artery and vein are cut. The pancreas with the duodenum and spleen is removed after cutting the gastroduodenal artery.

In the majority of IAT centers, the pancreas is transported along with duodenum and spleen for islet isolation. In Baylor University Medical Center, specially trained islet specialists are involved in the organ procurement, trimming the organ, and performing pancreatic ductal cannulation. This procurement procedure is performed under cold condition for the purpose of shortening the warm ischemic time. The trimmed pancreas alone is placed in the cold preservation solution and transferred to an islet processing facility clean room. During the time of islet isolation, reconstruction is performed in the operating room, including choledochojejunostomy and duodenojejunostomy. Galvani et al. reported on a fully robotic-assisted TP followed by IAT, allowing safe vascular dissection and reconstruction of the digestive tract (Galvani et al. 2014; Gruessner et al. 2014).

Pancreatic Islet Isolation for Autologous Transplantation

Pancreatic islets occupy approximately 2–5% of the volume of the pancreas in healthy adults (Foulis 1993). The techniques of pancreatic islet isolation for clinical islet autotransplantation have been developed based on those designed for allogeneic islet transplantation using a brain-dead donor who has a healthy pancreas. The major components of the pancreatic islet isolation process consist of enzymatic digestion of the pancreas and optional density-gradient purification and assessment of isolated islets (Ricordi et al. 1989). The condition of the resected

pancreas is a critical factor in the outcome of islet isolation (Ricordi et al. 1989). Structural damage to the pancreatic tissue including severe fibrosis, calcification, and prior distal pancreatectomy are more commonly encountered during the assessment of pancreatic status in TPIAT than in the setting of a carefully chosen healthy donor pancreas for allogeneic transplantation. Each step involved in the islet isolation such as enzyme perfusion, pancreas digestion, and islet purification should be optimized for the individual CP patient. The technical approaches of islet isolation for clinical islet autotransplantation are presented below.

Enzyme Perfusion into Chronically Inflamed Pancreas

After decontamination of the procured pancreas with polyvinylpyrrolidone, antibiotics, and/or antifungal drugs followed by extensive washing with Hank's Balanced Salt Solution (HBSS), perfusion of collagenase enzyme is the first step of pancreatic islet isolation (Bucher et al. 2005). In a pancreas with minimal change due to CP, the pancreatic duct system should be maintained intact and collagenase solution can be distributed into the whole pancreas as in a healthy organ. Many islet institutes have implemented semiautomated enzyme perfusion with a peristaltic pump for 10 min in cold temperature to prevent premature activation of the collagenase enzyme. Optional manual injection of collagenase solution into the pancreas parenchyma is considered for severely fibrotic organs when distension of the pancreas during the semiautomatic enzyme perfusion is not sufficient. For this reason, the distension of the pancreas during enzyme perfusion should be carefully monitored and recorded to evaluate the quality of enzyme distribution (Sakuma et al. 2008; Takita et al. 2010).

Of note, several collagenase enzymes are commercially available for pancreas digestion in clinical islet autotransplantation. A mixture of collagenase derived from *Clostridium histolyticum* (Ch) and neutral protease(s) derived from the same microorganism or *Bacillus thermoproteolyticus rokko* are commonly used. Balamurugan et al. determined the efficacy of different combinations of collagenase and neutral proteases for clinical islet autotransplantation. They showed that the isolated islet yield was maximized when intact class 1 collagenase and neutral protease with Ch was used (Balamurugan et al. 2012).

Digestion of Pancreas

The pancreas perfused with cold collagenase enzyme is cut into approximately 9–11 small pieces of 2–4 cm length before the digestion process. The pieces of pancreas and the enzyme solution are placed in the Ricordi chamber. The pancreatic tissue is digested with activated collagenase during circulation in a closed circuit with a Ricordi chamber and a warm water bath. The digestion temperature is maintained between 30 °C and 37 °C. Light marbles in the Ricordi chamber exert mechanical force to aid the digestion process. At regular intervals of 2–4 min apart, an aliquot of the enzyme solution is used to measure released islets. The enzymatic digestion of the pancreas is discontinued after optimal release of islets is observed in the test samples. In the case of a severely damaged pancreas, the number of islets released may be less than that for a normal organ. Digestion time is determined based on both microscopic observation of digested tissue samples and macro changes in the size of the pancreatic mass in the Ricordi Chamber. Technical experience of the team involved in the isolation process is critical for successful isolation of high-quality islets.

Optional Islet Purification

The purpose of IAT is to return as many of a patient's own islets as possible to maximize the opportunity to retain pancreatic endocrine function. At the completion of the enzymatic digestion of the pancreas, it is common to obtain a compacted cell volume of greater than 20 ml. Since infusion of a large volume of packed pancreatic tissue into the liver could result in portal vein thrombosis, it is essential to purify islets from the whole digest. Islet purification is an optional procedure since a significant mass of islets can be lost during the purification process. The

University of Minnesota group has reported that the final tissue volume that is transplanted is an independent predictor for the elevation of portal vein pressure during islet infusion. They proposed a target tissue volume of less than 0.25 ml/kg of patient body weight (Wilhelm et al. 2013).

Islets are purified using a density gradient centrifugation method and a cell separator such as a COBE 2991 processor. After the centrifugation, islets and acinar cells are distributed in lighter and heavier density layers, respectively. Some islet transplant centers use islet purification with a fixed density of high- and low-gradient solution, while others employ purification with a continuous gradient solution after adjusting for the optimal density of each pancreatic digest (Anazawa et al. 2011). The benefit of islet purification with density-adjusted continuous gradient solution is to minimize islet loss. A significant benefit of islet purification is the elimination of acinar tissue, which is known to negatively impact islet function.

Remote Site Processing

Pancreases of CP patients exhibit large variation from minimal change from healthy to severely fibrotic "rock-like" pancreases. Some patients with CP have a history of previous pancreatic surgery such as Peustow's procedure, Whipple procedure, and distal pancreatectomy before TPIAT. Every islet isolation procedure in clinical islet autotransplantation should be customized for each patient based on the above description. Hence, well-experienced islet specialists should be in charge of the isolation process. From a regulatory point of view, the current good tissue practice (cGTP) has to be followed during the entire tissue manufacturing process. As a result, access to islet isolation facility is limited. The remote site processing is an alternative way to broaden the opportunity of TPIAT to patients with severe CP who are not at an islet isolation facility. A fruitful collaboration between the University of California at Los Angeles for surgery and University of California at San Francisco for islet isolation was recently reported (Tai et al. 2014).

Islet Infusion

Islet Infusion into Hepatic Portal Vein

The isolated islets are suspended in sterile transplant medium and packed in a specially designed infusion bag along with a low dose of heparin (70 units/kg body weight of the patient). The bag method is a commonly performed procedure for islet infusion into the hepatic portal vein since the infusion rate is manageable during continuous natural dripping by gravity. Elevation of portal vein pressure to excessive levels (>22 mmHg) can be prevented by reducing or temporal discontinuation of islet infusion. Portal vein pressure should be carefully monitored during the infusion. During the early years of TPIAT procedures, isolated islets were placed in a syringe and directly injected into the portal vein. This approach carried a risk of unintended high portal vein pressure.

Route of Islet Infusion

Several routes are available for autologous islet infusion into the hepatic portal vein. The common route is cannulation into the portal vein from the superior mesenteric vein branch before skin closure. Transhepatic cannulation with interventional radiology after the operation is an alternative way. The University Hospitals of Leicester has reported a new approach of islet infusion using the umbilical vein (Ong et al. 2009).

Peritransplant survival of islet autograft

Following transhepatic intraportal infusion of islets, a strong nonspecific inflammatory response has been shown to occur in TPIAT patients (Naziruddin et al. 2014a). This response has been termed as "instant blood-mediated inflammatory response" (IBMIR) and is primarily triggered due to the incompatibility between isolated islets and blood. Mechanisms underlying this damaging response are unclear. It has been shown that IBMIR in TPIAT patients is

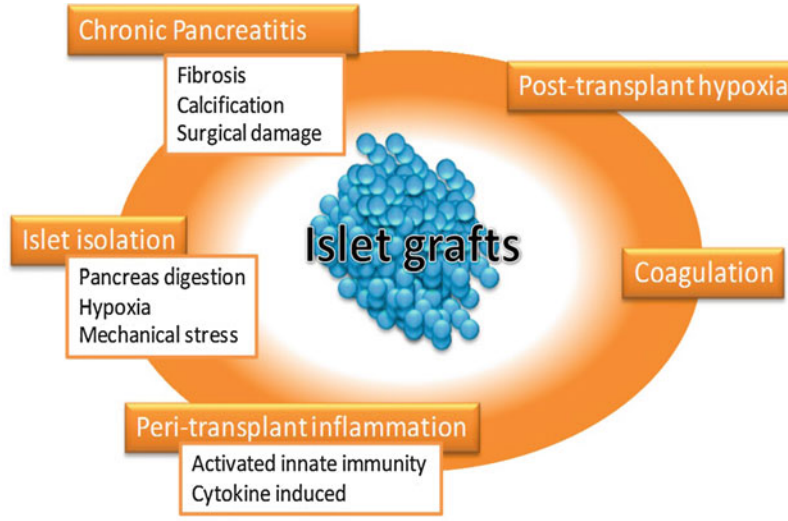

Fig. 2 Factors that influence quality, quantity, function, and survival of islets in TPIAT

characterized by concomitant release of inflammatory mediators (such as TAT, IL-6, IL-8 and IP-10) and C-peptide. When islets were mixed with autologous blood under in vitro conditions, expression of MCP-1 increased dramatically in the islets, indicating its significant role as a mediator of islet damage (Kanak et al. 2014a). Furthermore, islets infused into liver experience other damaging events (illustrated in Fig. 2), which include hypoxia, oxidative stress, and proinflammatory response (Kanak et al. 2014b).

Clinical Outcome

The main purposes of TPIAT are to eliminate intractable abdominal pain by total pancreatectomy, to preserve pancreatic endocrine function by returning autologous islets, and in turn, to improve the quality of life of CP patients. Several reports from IAT centers have been published to show their clinical results. Table 2 provides a summary of data from major TPIAT centers.

Patient Survival

According to the University of Minnesota, which has performed more TPIAT than any other center, the five-year survival rate after surgery was 90% including adults and children (n=409) (Sutherland et al. 2012). The Leicester group reported that survival rate after TPIAT was significantly longer than total pancreatectomy alone although the clinical study is not a randomized trial (16.5 and 12.9 years in TPIAT and TP-alone groups, respectively $p < 0.01$) (Garcea et al. 2013).

Impact of TPIAT in Endocrine Function

A major purpose of IAT is to return as many of the patient's own pancreatic islet cells as possible to the patient. The amount of islets transplanted, assessed by islet equivalents (IEQ), has been reported to correlate with glycemic control after TPIAT. Sutherland et al. reported that the proportions of recipients who achieved insulin independence one year after TPIAT are 7%, 27%, and 63% for recipients who were transplanted with less than 2500 IEQ/kg, 2500–5000 IEQ/kg, and more than 5000 IEQ/kg, respectively (Sutherland et al. 2008).

Pain control

Elimination of severe abdominal pain is the major advantage of TP. Major centers have reported that

Table 2 Summary of current outcomes of TPIAT

Center	Pain outcome	Diabetes outcome
University of Minnesota (Sutherland et al. 2012)	59% became narcotic free 24 months after TPIAT although all patients were narcotic dependent before TPIAT	22% achieved insulin independence 36 months after TPIAT if the patients received 2500–5000 IE/kg
University of Cincinnati (Wilson et al. 2013)	79% became narcotic free 9 months after TPIAT	29% achieved insulin independence 9 months after TPIAT (mean islet dose: 7437 IEQ/kg)
University of Alabama (Argo et al. 2008)	60% became narcotic free 6 months after TPIAT	No patient achieved insulin independence 6 months after TPIAT (mean islet dose: 1551 IEQ/kg)
Medical University of South Carolina (Morgan et al. 2012)	23% became narcotic free 12 months after TPIAT	24% achieved insulin independence 12 months after TPIAT (mean islet dose: not reported)
University Hospital of Leicester (Garcea et al. 2009, 2013)	42% became narcotic free 60 months after TPIAT	24% achieved insulin independence 12 months after TPIAT (mean islet dose: not reported)
Baylor (Naziruddin et al. 2014b)	70% became narcotic free 12 months after TPIAT	35% achieved insulin free 12 months after TPIAT (mean islet dose: 5438 IEQ/kg)

more than half of the patients became narcotic independent although there is variation in the results between institutes performing TP (Table 2). Long-term follow-up is warranted to justify pain outcomes since pain due to the surgical procedure, including skin incision, can affect the results.

Conclusion

TPIAT has shown tremendous promise for the treatment of patients with severe CP not only in terms of achieving relief from intractable pain but also for prevention of surgically induced diabetes. Improvements in the assessment of CP severity based on laboratory tests, image analysis, and a multidisciplinary team have played a central role in the selection of appropriate candidates for TPIAT. Development of unified criteria for early diagnosis and treatment will minimize pancreatic damage, which in turn will lead to better results with the islet isolation process and improved transplant outcome. The process of isolating islets is undergoing subtle changes to improve the mass of isolated islets. These include improving the pancreas procurement and preservation steps, purification of islets using islet-friendly gradient solutions, and incorporation of anti-inflammatory solutions. While the liver is the site most commonly used for islet autotransplantation, several hurdles remain to be overcome to improve survival of transplanted islets. These include minimization of damage due to IBMIR, hypoxia, endoplasmic reticulum stress, and islet exhaustion. Since the isolation procedure requires technical expertise and adherence to cGTP conditions, the practice of TPIAT is still limited to select centers. The introduction of potent anti-inflammatory therapy at least during the peritransplant period should improve islet survival. A major objective of the TPIAT procedure is to improve the quality of life (QoL) of CP patients, and several published reports have already indicated significant improvement in the QoL of TPIAT patients. However, a comprehensive multicenter trial is essential to draw firm conclusions. Finally, the cost of TPIAT is considered prohibitive for its broader application to many qualified patients. Policies that will make it affordable and thus increase the number of TPIAT surgical procedures will also lead to the development of innovative approaches to further significantly improve the outcomes.

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Surgical Complications of Pancreas Transplant

Muhammad Irfan Saeed

Contents

Abstract

Pancreas transplantation provides diabetic patients a means of achieving normoglycemia, improving their quality of life and preventing secondary complications of diabetes mellitus. Pancreas transplant is considered a quality of life improving procedure. Compared to liver, heart, and lung transplants which are life-saving procedures, an improved quality of life comes with the cost of potential morbidity related to the operation and the requirement of life-long immunosuppression.

Keywords

Pancreas complications · Graft thrombosis · Urological complications · Acute rejection · PTLD

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Introduction

Gruessner compared the mortality of pancreas transplant recipients to patients on the pancreas waiting list using data provided by United Network for Organ Sharing (UNOS) and International Pancreas Transplant Registry (IPTR) (Gruessner et al. 2004). Multivariate analysis showed that overall mortality in all three transplant categories (simultaneous pancreas kidney [SPK], pancreas after kidney [PAK], and pancreas transplant alone [PTA]) was not increased after transplantation and was significantly decreased for SPK recipients ($p = <0.001$). Humar studied the incidence of early mortality (less than 3 months after transplant) and demonstrated a significant decrease in the surgical risk associated with this procedure (Humar et al. 1999). Reasons for decreased risk included identification of donor and recipient risk factors, better prophylaxis regimens, surgical technique refinements, and improved immunosuppression. Pancreas transplant patient survival at 1 year and 5 years is currently around 95% and 88%, respectively. Graft survival at 1 year and 5 year is near 85% and 60%, respectively (Gruessner et al. 2011) (Figs. 1, 2, 3, 4, 5, and 6).

Complications after pancreas transplant can be classified as early or late, depending on the timing of onset relative to transplantation (Table 1).

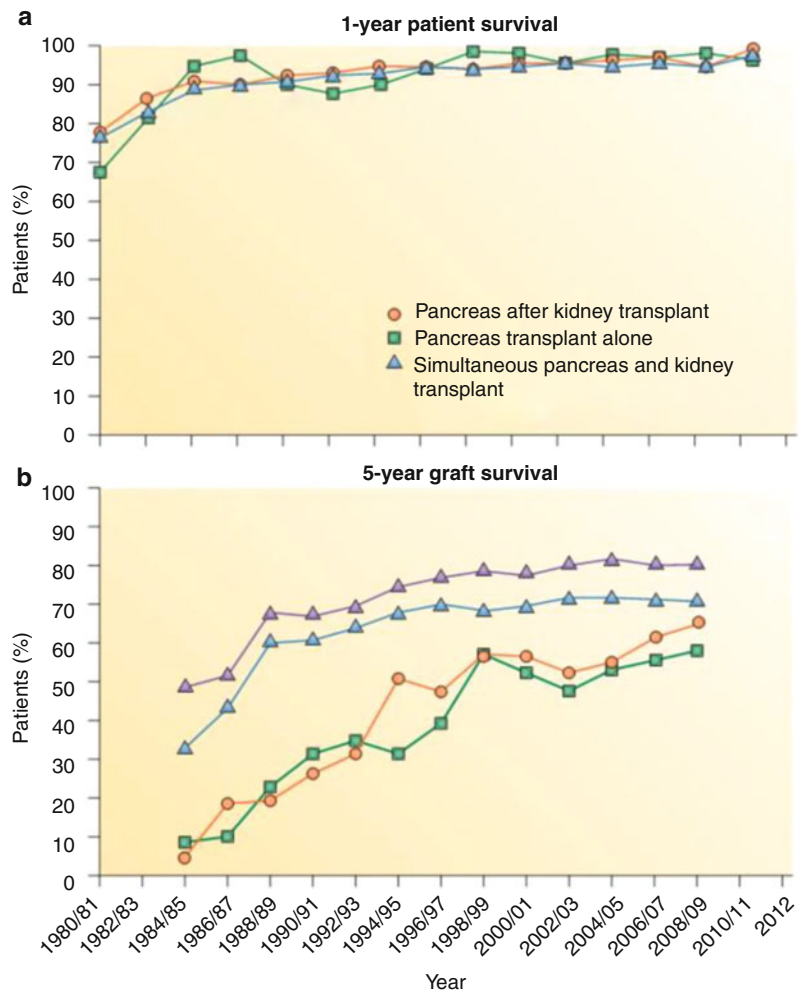

Fig. 1 Patient survival after pancreas transplantation over time. (**a**) 1-year posttransplant survival. (**b**) 5-year posttransplant survival (Data were obtained from the International Pancreas Transplant Registry and the United Network for Organ Sharing)

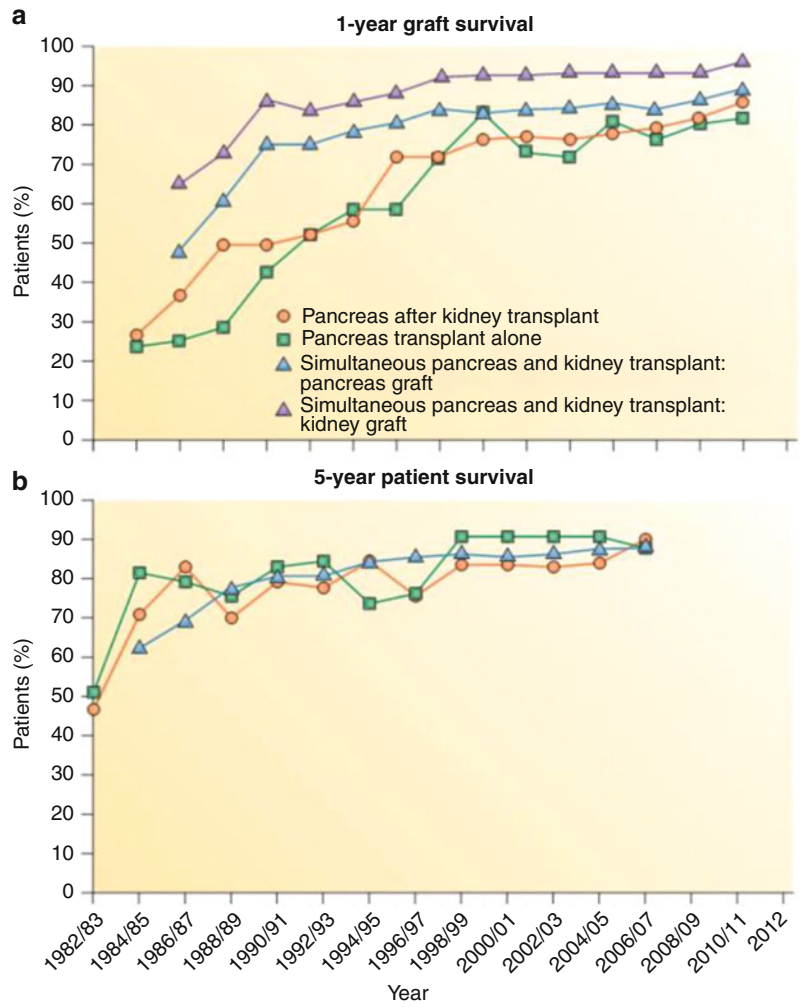

Fig. 2 Pancreas graft survival over time. (**a**) 1-year posttransplant graft survival. (**b**) 5-year posttransplant graft survival (Data were obtained from the International Pancreas Transplant Registry and the United Network for Organ Sharing)

Vascular Complications

Pancreas Graft Thrombosis

Vascular complications include graft thrombosis, arterial stenosis and kinks, pseudoaneurysm formation, arteriovenous fistulae, vessel injury due to surgical technique (clamp injury), and underlying atherosclerotic disease (Chandran et al. 2013). Overall, graft thrombosis incidence ranges from 3% to 10%. The most common reason for early graft loss due to nonimmunological reasons is graft thrombosis.

Both arterial and venous thrombosis are known complications, but venous thrombosis occurs twice as frequently (Farney et al. 2012). Thrombosis can be partial versus complete or early versus late. Risk factors for early pancreas graft thrombosis can be classified in relation to the donor, recipient, or underlying disease (diabetes) (Schenker et al. 2009; Farney et al. 2012). Donor factors include age $>$ 50 years, BMI $>$ 30 kg/m^2, and cardiovascular cause of death (Kandaswamy et al. 2004). Recipient factors included inherited hypercoagulable states, age $>$ 50 years, BMI $>$ 30 kg/m^2, cardiovascular disease, and left-sided graft placement (Kandaswamy et al. 2004; Troppmann et al. 2010; Lubezky et al. 2013). Other factors related to thrombosis are prolonged cold ischemia time greater than 24 h (Parr et al.

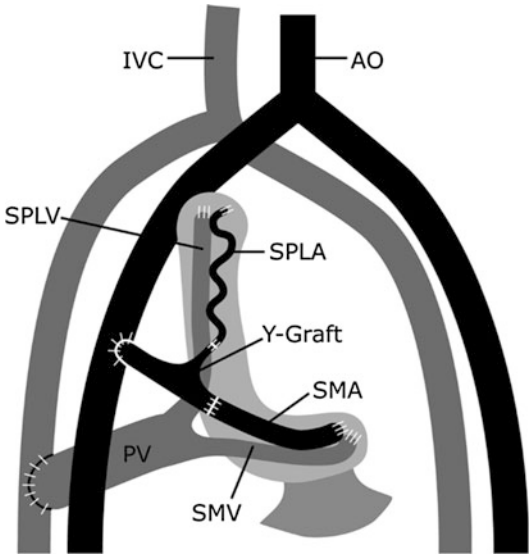

Fig. 3 Surgical arterial anatomy in systemic bladder-drainage pancreatic transplant. As shown, the base of Y graft anastomosis is end-to-side with the recipient common (CIA) or external iliac artery (EIA). The superior mesenteric artery (SMA) perfuses the head and neck of the pancreas, whereas the splenic artery (SPLA) perfuses the body and tail. The relationships with portal vein (PV), superior mesenteric vein (SMV), splenic vein (SPLV), aorta (AO), internal iliac artery (IIA), and inferior vena cava (IVC) are additionally depicted

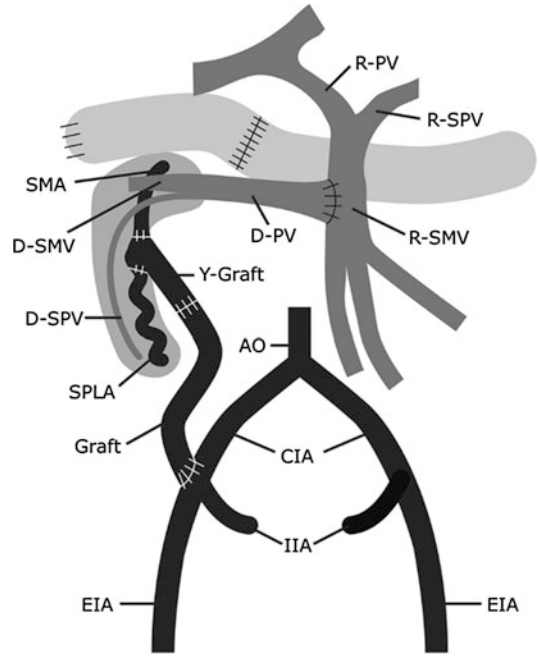

Fig. 4 Surgical arterial anatomy in portal-enteric-drainage pancreatic transplants. As shown, the base of the Y graft anastomosis is end-to-side with the recipient CIA, but it is much longer due to its location in the abdomen. The superior mesenteric artery (SMA) perfuses the head and neck of the pancreas, whereas the splenic artery (SPLA) perfuses the body and tail. The relationships with donor PV (D-PV), donor SMV (D-SMV), donor SPLV (D-SPLV), recipient PV (R-PV), recipient SMV (R-SMV), and recipient splenic vein (R-SPV), aorta (AO), and inferior vena cava (IVC) are additionally depicted

2000), hypotension, segmental pancreas transplant, and postoperative graft pancreatitis (Kandaswamy et al. 2004; Troppmann et al. 2010; Lubezky et al. 2013). Muthusamy explained the pathophysiology of graft thrombosis based on Virchow's triad (Muthusamy et al. 2010) (Table 2).

Diabetes itself is a hypercoagulable state, and many diabetics experience a thrombotic event in their lifetime (Miller 1993; Carr 2001; Wullstein et al. 2003). Furthermore, acute surgical stress induces a transient hypercoagulable state (Muthusamy et al. 2010). Patients with inherited thrombophilic disorders, including deficiencies of natural anticoagulants such as antithrombin III and protein C or S and factor V Leiden and prothrombin mutations, likely contribute to the risk of graft thrombosis (Muthusamy et al. 2010). Endothelial damage leads to a procoagulant milieu and damage can occur secondary to ischemia reperfusion injury. Other factors contributing to graft thrombosis are high dose calcineurin inhibitors (cyclosporine > tacrolimus), type of preservation solution (UW vs. HTK), large flush volume, postoperative pancreatitis, smoking, and obesity. Back-table reconstruction of vessels (arterial) or placement of venous extension graft also contributes to endothelial injury (Farney et al. 2012). Pancreas graft thrombosis is also associated with administration of immunoglobulin IVIG (Sinha et al. 2009). Drainage of the portal vein into the superior mesenteric vein versus a systemic vein (i.e., inferior vena cava versus iliac vein) does not seem to alter the risk of thrombosis. The use of vasopressors was significantly associated with early pancreas graft thrombosis on univariate and multivariate analysis ($p = 0.04$, CI 1.11-68.9) (Schenker et al. 2009).

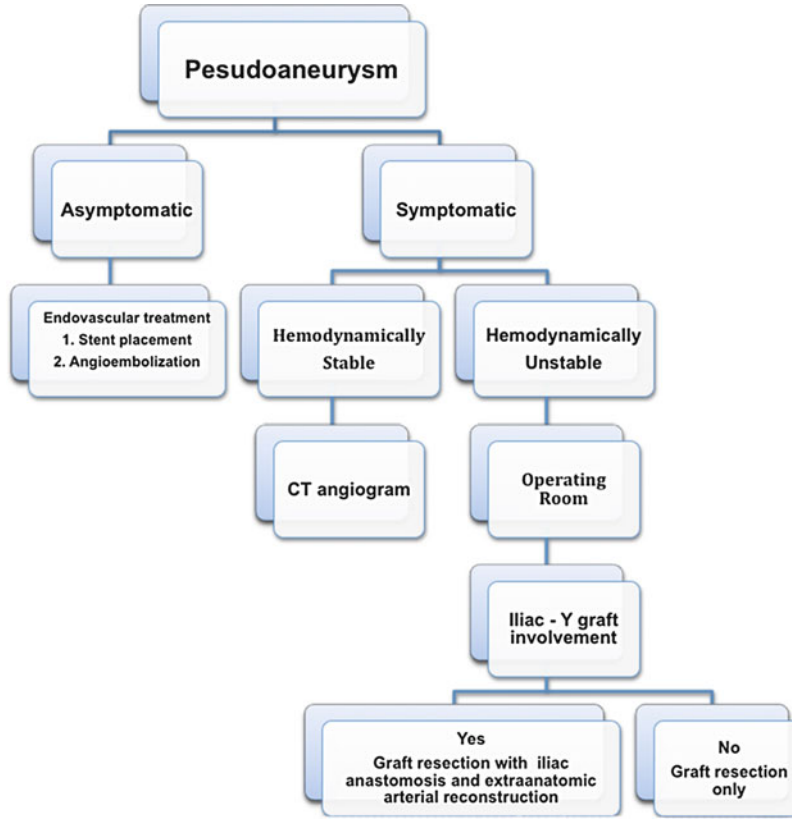

Fig. 5 Management of pseudoaneurysm

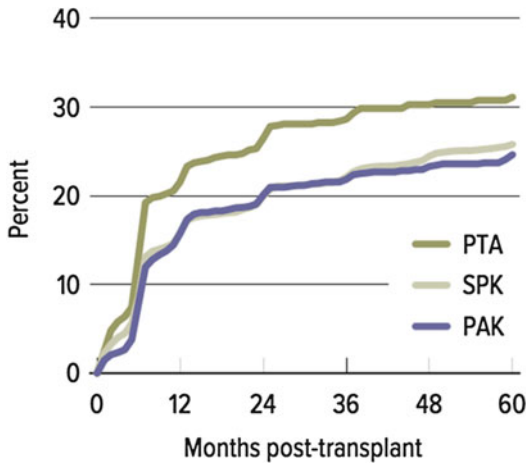

Fig. 6 Incidence of first acute rejection among adult patients receiving a pancreas transplant from 2006 to 2010

Blood glucose concentrations should be monitored frequently during the first 24–72 h after pancreas transplant when risk of thrombosis is highest. A spike in blood sugars suggests the possibility of thrombosis, while elevation of pancreatic enzymes beyond 5 days posttransplant has been cited as an independent risk factor for graft thrombosis (Fertmann et al. 2006). Graft tenderness and enlargement, dark massive hematuria (in bladder-drained pancreas), and markedly decreased urine amylase levels are suggestive of thrombosis (Troppmann et al. 2010). Color Doppler ultrasound is considered the first tool for diagnosis. It is easy to perform and noninvasive, features that make it particularly useful for timely intervention or surveillance of the pancreas graft (Morelli et al. 2008). Each transplant center has its own protocol for surveillance starting from postoperative day 1 and continuing for several days postoperatively. Foshager retrospectively reviewed their center's data and found that absence of antegrade diastolic flow and resistive index (RI) > 1 was 100% sensitive for detection of graft thrombosis (Foshager et al. 1997). Diastolic flow reversal with RI > 1 in the pancreatic allograft artery during the first 12 days after

Table 1 Complications postpancreas transplant

Early	Late
1. Vascular complications	1. Rejection (chronic)
2. Bleeding	2. Vascular complications
3. Leak (intestinal or bladder) anastomosis	3. Intestinal obstruction
4. Rejection	4. Malignancy
5. Graft pancreatitis	5. Infectious complications
6. Infectious complications	6. Immunosuppression
7. Primary nonfunction	
8. Delayed graft function	

Table 2 Factors in pancreas transplant thrombosis classified according to Virchow's triad

Hypercoagulability	Vessel wall changes (endothelial activation)	Changes in flow
Diabetes	Ischemia-reperfusion injury	Altered splenic vein flow dynamics
Surgical stress	Calcineurin inhibitors	Venous outflow (iliac versus caval, left versus right side)
Hyperlipidemia	Overperfusion with preservation solutions	
Inherited thrombophilic disorders	Preexisting vascular disease	
Platelet abnormalities	Pancreatitis	

transplantation was highly specific for venous thrombosis, especially in the absence of venous flow. Computed tomography (CT) and magnetic resonance imaging have also been performed for diagnosis but are less readily available and more costly (Kim et al. 2012). If clinical and radiological data suggest thrombosis, it should be confirmed by angiogram (Friedll et al. 2012) (Table 3).

Most transplant centers utilize some form of anticoagulation for prophylaxis of vascular thrombosis following pancreas transplantation. The choice of anticoagulant, dose, and duration of treatment is typically based upon risk stratification (Fertmann et al. 2006; Farney et al. 2012). Various combinations used include aspirin, dextran (Rheomacrodex, MEDA AS, Denmark), heparin, dipyridamole, and warfarin with varying outcomes (Table 4).

Complete venous or arterial thrombosis generally results in graft loss, but salvage by thrombectomy (surgical or percutaneous) has been described. Partial venous thrombosis (usually of splenic vein) has been managed successfully with anticoagulation alone. Choice of intervention depends upon patient condition (symptomatic versus asymptomatic), site and extent of thrombosis, operator experience, and availability of skilled interventional radiologists (Friedll et al. 2012). Venous thrombosis can propagate beyond the vascular anastomosis; mesenteric venous (if portally drained) and iliac vein or vena cava (if systemically drained) clots should be controlled and cleared to prevent venous insufficiency to the bowel or embolism, respectively (Farney et al. 2012).

Nonmodifiable donor risk factors for pancreas graft thrombosis include age, obesity, vascular disease, and donation after cardiac death. It therefore becomes extremely important to optimize modifiable risk factors like procurement technique, preservation solution (University of Wisconsin), minimization of preservation time, avoidance of high dose calcineurin inhibitors, and meticulous surgical technique. Screening for inherited hypercoagulable states may identify patients at high risk for thrombosis (Wullstein et al. 2003). Postoperative anticoagulation should be utilized, and clinicians should have a low threshold for intervention if thrombosis is suspected (Fridell et al. 2011).

Surgical options for thrombectomy include insertion of a Fogarty balloon catheter through the distal splenic vein or portal vein anastomosis to retrieve the thrombus. Partial pancreatectomy may be a salvage procedure in the setting of a partial thrombus. Endovascular thrombectomy may be attempted for treatment of partial thrombosis (MacMillan et al. 1998; Matsumoto 2011; Saad et al. 2012). Occasionally, surgical intervention is

Table 3 Duplex sonographic criteria for diagnosis of pancreatic transplant venous thrombosis

Sonographic criteria	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Arterial RI $\geq$ 1.00	100	88	69	100
Arterial RI $>$ 1.00	73	95	80	93
Absent intrapancreatic venous flow	100	100	100	100
Arterial RI $\geq$ 1.00 and absent intrapancreatic venous flow	100	100	100	100

Note: *PPV* positive predictive value, *NPV* negative predictive value, *RI* resistive index

Table 4 Anticoagulation measures and thrombosis rates in pancreas transplantation

Source	Intervention	Thrombosis (%)	Bleeding (%)
Sollinger et al.	None	0.8	0.8
Humar et al.	7,500–12,000 U UFH + 325 mg aspirin	6.8	$<$1
Burke et al.	TEG; UFH/aspirin/dextran/warfarin	1	2
Dafoe et al.	Pancreaticorenal composite graft (case report)	–	–
Fertmann et al.	Antithrombin III/IV UFH	16	No difference
Vaidya et al.	TEG; 75 mg aspirin/dextran/UFH/LMWH/ warfarin	0	1.3
Schenker et al.	LMWH	7	6.9

deferred if there is evidence of collateral flow to the pancreas allograft (Kuo et al. 1997; MacMillan et al. 1998; Friedll et al. 2012).

Several investigators have debated the optimal strategy for venous drainage of the pancreas allograft: systemic (via the inferior vena cava or iliac vein) versus portal (via the superior mesenteric vein) (Gaber et al. 1995; Laftavi et al. 2014). Petruzzo compared the two techniques and did not find any significant difference in graft survival, rejection, hyperinsulinemia, or lipid metabolism (Petruzzo et al. 2000). On the contrary, Philosophe concluded that graft survival and rejection were better with portal drainage (Philosophe et al. 2001). These investigators found that systemic drainage caused hyperinsulinemia, which led to accelerated atherosclerosis, independent of the dyslipidemic effects of immunosuppressant.

Bleeding

The impact of postoperative bleeding on graft survival is comparatively benign, as only 0.3% of pancreas grafts are lost secondary to bleeding (Troppmann et al. 2010). Immediate postoperative bleeding is often due to perioperative anticoagulation. Once bleeding or a significant hematoma is diagnosed, the underlying abnormality should be corrected. The recipient should undergo reexploration because a large hematoma can serve as an ideal medium for bacterial growth. A large hematoma can cause external compression on venous outflow or kink the arterial graft. Evacuation of the hematoma can be therapeutic in itself, even if no surgical bleeding is found on reexploration.

Early postoperative vesical bleeding can manifest as hematuria, which is usually self-limiting. Late hematuria is secondary to complications such as graft biopsy or arteriovenous fistula; in those cases most patients will need conversion to enteric drainage (Troppmann et al. 2010). Gastrointestinal bleeding causes in the early and late postoperative period are listed in Table 5. Massive bleeding should be aggressively investigated with a contrast CT scan, and/or emergent intervention (Table 5).

Other Vascular Complications

Besides vascular thrombosis, other vascular complications include development of an arterial pseudoaneurysm, arteriovenous fistula (Dematos

Table 5 Bleeding causes postpancreas transplant

Early postoperative GI bleeding	Late postoperative GI bleeding
1. Duodenal bleeding	1. Ischemic duodenal ulcer
2. Enteric anastomotic	2. Duodenal CMV infection
	3. Acute or chronic duodenal rejection
	4. Duodeno-jejunal anastomosis
	5. Duodenitis
	6. Neoplasm (colonic)
	7. Entero-arterial fistula (massive)

Table 6 Etiological causes of pseudoaneurysm formation

Infectious	Noninfectious
1. Intraabdominal/ wound infection	1. Percutaneous/ transcystoscopic needle biopsy
a. Anastomotic leak (bowel/bladder)	2. Pancreatitis
b. Infected hematoma	3. Procurement injury/back-table injury
c. Wound infection	4. Clamp injury to recipient or donor vessels
d. Bacteremia or candidemia	5. Congenital anomaly

et al. 2000; Barth et al. 2008), arterial stenosis, and arterial dissection (Woo et al. 2003; Tsuchiya 2005). There are no large case series reported on these topics, rather individual case series. A graft pseudoaneurysm can present early (less than 3 months) or late (greater than 3 months) after transplantation. Predisposing factors leading to aneurysm formation are listed in Table 6.

Candida albicans infection can cause inflammatory arteritis, resulting in arterial necrosis (Akhtar et al. 2011). In patients developing infectious complications posttransplant, a Doppler ultrasound of the pancreas transplant is recommended (Kim et al. 2012). Stent placement should not be performed across potentially infected aneurysms due to stent erosion through infected wall and secondary stent infection. An open surgical approach is the preferred treatment for an infected aneurysm with extensive and aggressive toilet of the infected field and extra-anatomic bypass for revascularization (Akhtar et al. 2011). A multidisciplinary approach involving a vascular surgeon is important in managing these complex cases.

Humar et al. found the incidence of deep venous thrombosis (DVT) among SPK and kidney transplant alone patients was 18.1% versus 4.5%, respectively (Humar et al. 1998). In the case of SPK patients, DVTs occurred more commonly on the side of the pancreas versus the kidney allograft. Allen observed two peaks in the timing of thrombosis occurrence: one in the first postoperative month and a second in the fourth month posttransplant (Allen et al. 1987). The second peak most likely represented the time required for resolution of the effect of uremia on erythropoiesis and platelet function. Increased risk of DVT is associated with bilateral dissection of the iliac vessels, longer operative/recovery times, recipient age > 40 years, previous DVT, diabetes mellitus, pelvic dissection, and low flow in the pancreatic venous system. Graduated compression stockings and low dose heparin are routinely recommended for prevention of DVT. Early ambulation is highly recommended postoperatively as well (Humar et al. 1998).

Anastomotic Leak

Anastomotic leaks are responsible for almost 0.5% of all graft losses. The incidence of graft loss is higher with enteric-drained versus bladder-drained pancreas transplants (Troppmann et al. 2010). In enteric-drained pancreas allografts, a leak will present with peritonitis and sepsis due to spillage of enteric contents. In the case of bladder-drained pancreas allografts, leaks are associated with a lower rate of infectious complications.

Symptoms of anastomotic leak include abdominal pain, peritonitis, ileus, fever, leukocytosis, decreased urine output, and hyperamylasemia. Enteric leak can be classified as early (<4 weeks) or late (>4 weeks). Early leaks are usually due to technical failure or ischemia versus late which are due to rejection or infection. Abdominal CT with oral contrast is used to make diagnosis. Treatment includes relaparotomy with

conversion of side-to-side duodeno-jejunostomy to a Roux-en-Y duodeno-jejunostomy. Transplant pancreatectomy is indicated in the presence of diffuse intraabdominal infection or if the patient is unstable.

Bladder-drained graft leaks are divided into early (<4 weeks) and late (>4 weeks). Symptoms are nearly the same as previously described for enteric leaks. CT scan of the abdomen/pelvis with retrograde bladder contrast makes the diagnosis. Low pressure cystography can also be performed, but the former study is more accurate. In early leak cases, prolonged Foley catheter drainage and percutaneous drainage of intraabdominal collections by interventional radiology is therapeutic. If the patient shows signs of peritonitis, then relaparotomy is performed for repair or pancreatectomy. For late leaks, conversion from bladder to enteric-drainage is indicated, irrespective of the etiology (Troppmann et al. 2010).

Graft Pancreatitis

There is no uniformly accepted definition for posttransplant pancreatitis (early or late). Serum markers like amylase and lipase correlate poorly with the severity of graft pancreatitis. Risk factors associated with early postoperative graft pancreatitis include donor quality (age, obesity, history of prolonged resuscitation, excessive inotropic requirements), use of HTK solution (especially when preservation time exceeds >12 h) (Rigley et al. 2008), prolonged preservation time, pancreatic duct outflow impairment, and bladder drainage (reflux pancreatitis). Complications of graft pancreatitis include peripancreatic abscess, pancreatic necrosis (sterile or infected), pancreatic fistulae, pseudocyst, and pseudoaneurysm formation (Akl et al. 2011).

Clinical presentation of graft pancreatitis includes abdominal pain, graft tenderness, nausea, vomiting, ileus, and elevation of serum amylase and lipase. A CT scan with IV contrast of the abdomen/pelvis should be performed to assess the pancreas, for signs of inflammation or necrosis.

Treatment of pancreatitis includes NPO status, bowel rest, and for selected cases, administration of total parenteral nutrition (TPN). The utility of octerotide (a somatostatin analogue) for prevention and treatment remains to be proven. Reflux pancreatitis in bladder-drained pancreas allografts is treated with insertion of a Foley catheter. If repetitive episodes occur, enteric conversion is indicated.

Infections

Postoperative infections can range from superficial wound infections to deep intraabdominal infections. In addition, posttransplant patients are always at risk for bacterial, viral, and fungal infections due to their immunocompromised status (Heitzman et al. 2011).

Superficial wound infections are treated using standard surgical wound care principles. On the other hand, deep wound infections (intraabdominal) present a serious problem. They usually occur within the first 30 days posttransplant. Of all deep infections, 50% are diffuse and 50% are localized. Up to 30% of infections are associated with an anastomotic leak (duodeno-enterostomy or duodeno-cystostomy). Risk factors for intraabdominal infection include older donor age, postoperative bleeding requiring relaparotomy, retransplantation, pretransplant peritoneal dialysis, extended preservation time, graft pancreatitis, and immunosuppression with sirolimus (Heitzman et al. 2011). In clinically stable patients, a CT scan may define the extent and nature of the infection. For bladder-drained grafts, retrograde contrast is used. The differential diagnosis should always include graft thrombosis and anastomotic leak, the treatment options of which were already outlined.

Treatment of the infection depends upon the patient's condition and the underlying cause. If the patient is clinically stable and has a localized intraabdominal infection, then antibiotics with percutaneous drainage is reasonable first-line therapy. If conservative therapy fails, or the patient deteriorates or becomes clinically unstable, relaparotomy is mandatory. If the patient presents with diffuse peritonitis, established surgical principles should be followed with resuscitation, broad-spectrum antibiotics, and surgical

intervention. Decision-making should focus on saving the patient's life versus graft salvage.

The dominant bacterial flora involved in postoperative infections includes Gram-negative bacteria (*Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Serratia marcescens*, and *Morganella morgani*) and Group-D streptococci (*Enterococcus faecium*, *Enterococcus faecalis*). Fungal strains include *Candida* species *C. albicans*, *C. galbrata*, and *C. krusei* (Heitzman et al. 2011). Cytomegalovirus (CMV) mismatch (CMV positive donor to CMV negative recipient) is an independent risk factor for infection. Urinary tract infections are more associated with female sex and bladder drainage of the pancreas graft (Herrero-Martinez et al. 2013). Clinical suspicion should be high for pathogens such as like tuberculosis, *Cryptococcus*, or West Nile virus if the transplant recipient lives in an endemic area.

Primary Nonfunction of Pancreas Graft

Primary nonfunction (PNF) is defined as the absence of graft function after other causes of early graft failure (e.g., vascular graft thrombosis or hyperacute rejection) are ruled out. The reported incidence of PNF is 0.5–1%.

Delayed Graft Function

Delayed graft function (DGF) is defined as the need for transient insulin administration during the early postoperative period; its incidence ranges from 3% to 69%. In the kidney transplant literature, DGF is associated with a higher incidence of rejection. In contrast, the incidence of pancreas transplant rejection is similar for recipients with and without delayed graft function.

Factors associated with DGF are recipient body weight > 80 kg, donor age > 45 years, and cardiocerebrovascular and nontraumatic cause of donor death. Pancreas transplant DGF is a clinical reality but remains poorly understood and warrants further study (Troppmann et al. 2010).

Rejection

Rejection episodes after pancreas transplant are a significant cause for immunological graft loss, though the incidence of rejection has decreased due to new immunosuppressant. The incidence of rejection is highest in pancreas transplant alone (PTA) and lowest in simultaneous pancreas kidney transplant (SPK).

OPTN/SRTR's (Scientific Registry for Transplant Recipients) 2012 annual report showed an increased incidence of acute rejection in PTA as compared to SPK or PAK. One theory that explains the higher incidence of rejection in PTA is that PTA recipients are in a healthier overall state and have a greater ability to mount a strong immune response. Moreover, identification of rejection is more challenging in PTA recipients because rising serum creatinine in SPK patients cannot be used as an early indicator of acute rejection.

Pancreas transplant biopsy is the gold standard for diagnosis of rejection. Drachenberg reviewed histological lesions and criteria for acute cellular and antibody-mediated rejection for pancreas transplant (Drachenberg et al. 2008).

Treatment of acute cellular rejection includes high dose corticosteroids and antithymocyte globulin, while acute antibody-mediated rejection is usually treated with a combination of corticosteroids, plasmapheresis exchange, intravenous immune globulin, and rituximab at most centers. The development of posttransplant donor-specific antibodies is associated with negative outcomes in pancreas transplant outcomes, including graft failure (Akl et al. 2011; Lorentzen et al. 2013; Kremers et al. 2013; Friend et al. 2014).

Malignancy

Solid organ transplant recipients are at increased risk of developing *de novo* malignancies. The most common malignancies include skin cancer, posttransplant lymphoproliferative disorder (PTLD), and Kaposi's sarcoma. Spanogle described the incidence and risk factors for skin cancer in pancreas transplant recipients; at 2, 5,

and 10 years posttransplant, the cumulative incidence of any skin cancer was 4.7%, 12.7%, and 19.6%, respectively (Spanogle et al. 2012). The cumulative incidence of squamous cell carcinoma was 2.8%, 10.3%, and 16.7%, respectively and for basal cell carcinoma was 2.4%, 7.8%, and 17.4%, respectively. Risk factors for skin cancer development include male sex, older age at transplantation, fair complexion, history of nonmelanoma skin cancer (NMSC), infection with the human papillomavirus (HPV), and pretransplantation diseases such as polycystic kidney disease and cholestatic liver disease (Otley et al. 2005; Nordin et al. 2007).

Kaposi's sarcoma, while relatively uncommon, is still 400–500 times more likely to occur in transplant recipients, being virtually absent in the general population.

Prevention is crucial to prevent malignancies in pancreas transplant recipients. This includes reduction in UV exposure (e.g., sun avoidance, UV-protective clothing, and sunscreen use) along with education and self-surveillance. Dermatologic evaluation by a trained health care professional is imperative, especially in patients with a history of skin cancer.

Posttransplant lymphoproliferative disorders include a spectrum of neoplastic diseases ranging from a benign polyclonal lymphoid proliferation resembling infectious mononucleosis to a highly aggressive monoclonal process such as diffuse B-cell lymphoma and disseminated extranodal lymphomas (Kruel et al. 2014). Most cases (80–90%) are of B-cell origin and are associated with Epstein-Barr virus (EBV) infection (Andiman et al. 1985). At least 90% of PTLD cases in solid organ transplants arise from recipient cells, in contrast to PTLD seen after bone marrow transplants (Kruel et al. 2014). PTLD incidence varies depending upon the organ transplanted, ranging from 0.5% in adult kidney or liver transplant recipients to more than 10% in lung, intestinal, and pediatric transplant recipients. As reported in their 2012 annual report, the OPTN/SRTR reported the incidence of PTLD in EBV-negative recipients to be 5%, 2%, and 1.1% in PTA, SPK, and PAK, respectively (Fig. 10). The increased incidence of PTLD in PTA recipients is likely secondary to their increased immunosuppression requirements. Caillard prospectively reviewed PTLD cases between January 1998 and December 2007 and found the cumulative incidence in kidney or kidney-pancreas transplant at 5 and 10 years was 1% and 2.1%, respectively (Caillard et al. 2012).

Risk factors associated with PTLD in a global cohort were age, EBV seronegativity, transplant time (before 2001), SPK transplantation, HLA mismatches, and use of T-cell depleting agents and azathioprine.

The link between EBV and PTLD was established in the early 1980s by Hanto et al. (1982, 1985) and is now widely recognized. The risk for PTLD was much greater in EBV-mismatched pairs (EBV donor/recipient); in contrast, EBV-negative lymphomas were associated with CMV mismatch, arguing for a putative role of another virus. Positive donor CMV serostatus was also associated with a greater risk of brain lymphomas (Caillard et al. 2012). Risk of early onset PTLD (within 12 months of transplant) is twofold higher in recipients with one or two HLA-B mismatches compared to those with no HLA-B mismatch (Caillard et al. 2005). A link between HLA-B mismatch and non-Hodgkin's lymphoma has previously been reported (Verschuuren et al. 2005). Lymphocyte-depleting induction therapy is associated with a 1.4-fold increase in the risk of PTLD. Subgroup analysis revealed that the risk of developing brain lymphomas is particularly high (fourfold higher) in patients who received T-cell depleting agents (Caillard et al. 2012). Cyclosporine was associated with an increased risk of graft lymphoma (RR = 2.7) but not with other types of PTLD. Azathioprine was associated with the development of lymphomas, particularly graft PTLD and EBV-positive lymphoproliferations. WHO classification of PTLD is shown in Fig. 8 (Taylor et al. 2005) (Figs. 7, 8, and 9).

Presenting symptoms of PTLD may be mild, resembling a mononucleosis-like syndrome (e.g., malaise, sweats, and fever). Unintentional weight loss and palpable or identifiable lymphadenopathy should prompt a biopsy, as histological analysis is key to diagnosis.

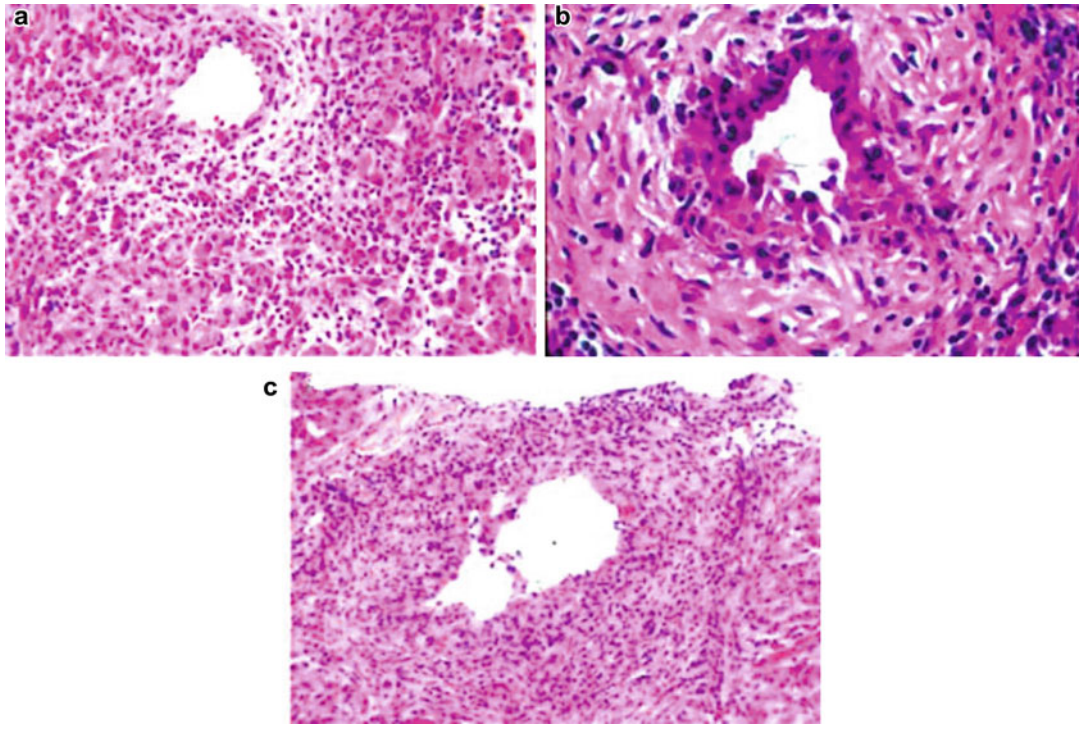

Fig. 7 Acute cell-mediated rejection (ACMR). (**a**) Active septal inflammation with numerous eosinophils and venulitis (*upper middle field*). (**b**) Ductal inflammation and associated reactive/regenerative epithelial changes. (**c**) Severe ductal inflammation. Dense infiltrates around a duct with extensive denudation of its epithelial lining. Few epithelial clusters on the *left upper contour* were positive for cytokeratin stain (not shown)

Treatment of early stages of PTLD may be effectively accomplished by reducing or discontinuing immunosuppression. Antiviral therapy with ganciclovir is controversial; however, other types or advanced stages of PTLD may require chemotherapy, radiation therapy, B-cell directed antibodies (e.g., rituximab), or resection.

Caillard reported graft survival of patients with lymphoma at 1 and 5 years to be 88% and 60%, respectively with treatment (Caillard et al. 2012). Overall PTLD patient survival was 73%, 60%, and 55% at 1, 5, and 10 years, respectively. Parasekevas compared the outcomes of PTLD in pancreas transplant recipients (n = 1357) to liver and kidney transplant recipients and found that pancreas transplant recipients had a significantly shorter survival ($p = 0.001$) (Paraskevas et al. 2005). Malignancies were more aggressive in pancreas recipients, with a higher stage at presentation and a trend toward more bone marrow involvement.

Hickey and associates advocate regular cystoscopic follow-up to rule out bladder cancer in all recipients of bladder-drained pancreatic transplants for 5 years posttransplant. Surgical therapy of bladder cancer should be aggressive (radical surgery with or without neoadjuvant/adjuvant radiotherapy and/or chemotherapy) and performed expeditiously (Highshaw et al. 2002).

Urological Complications

Urological complications after bladder drainage of the pancreas graft can be defined as directly related to the operation or indirectly related to the effect of pancreas transplantation on the lower urinary tract system (Gettman et al. 1996; Ciancio et al. 2000). Table 7 lists the urological complications found in pancreas transplantation.

Blanchet found a correlation between preoperative urodynamic abnormalities and the

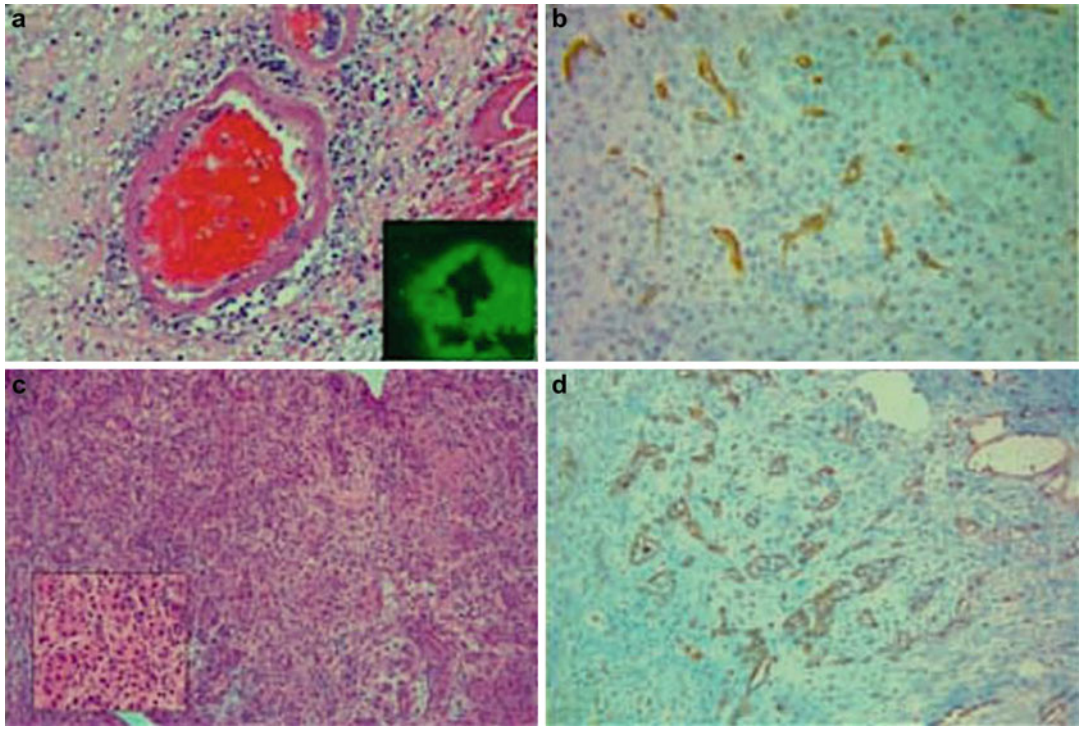

Fig. 8 Antibody-mediated rejection (ABMR). (**a**) Arterial fibrinoid necrosis due to accelerated AMR in a graft pancreatectomy performed 30 h posttransplantation. Insert: immunofluorescence stain is strongly positive for IgG. C4d stain (not represented) was also positive in all size vessels. (**b**) C4d stain in pancreatic capillaries in patient with acute AMR biopsied 10 days posttransplantation. (**c**) Same patient as part B, biopsied 18 days posttransplant, continues to have strong positivity for C4d (not represented) and extensive interacinar neutrophilic inflammation. Note foci of necrosis (*upper right*). (**d**) Same patient as parts B and C: strong C4d staining in pancreas lost due to persistent AMR, 3 months posttransplantation. Note extensive fibrosis with associated obliteration of the endocrine and exocrine components (chronic active AMR)

development of urological complications (Blanchet et al. 2003). Urodynamic abnormalities included large bladder capacity and a highly noncompliant and hypocontractile bladder with impaired proprioception and flow with postvoid residual urine. Gettman noted that criteria for abnormal preoperative urodynamics included detrusor hyperreflexia or areflexia (Gettman et al. 1996). Hyperreflexia is defined as uninhibited detrusor contraction with detrusor pressures of 15 cm H_2O or greater. Detrusor areflexia was defined as absent detrusor contractions or low pressure contractions accompanied by straining or stop-start voiding with a bladder volume of $>$ 600 cm^3, maximum flow less than 10 cm^3/s, and residual urine $>$ 150 cm^3. Indeterminate findings were defined as inconclusive detrusor pressures with normal bladder volume and maximum flow less than 10 cm^3/s and poor compliance or increased detrusor pressure 20 cm H_2O or greater over time without detrusor contraction.

Urinary tract infections are the most common urological complications with bladder-drained pancreas transplants. The most common organisms include *E. coli*, Group-D *Enterococcus*, *Staphylococcus epidermidis*, *Pseudomonas species*, *Proteus mirabilis*, or *Candida species* (Gettman et al. 1996). Patients are treated with intravenous or oral antibiotics depending on organism susceptibilities. Recurrent urinary tract infections can lead to drug resistance and frequent hospital readmissions.

Hematuria can be microscopic or gross and present early ($<$4 weeks) or late ($>$4 weeks)

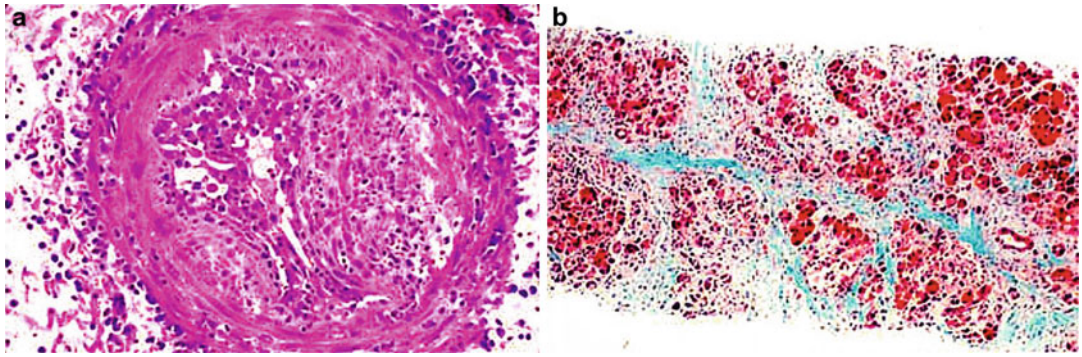

Fig. 9 Chronic rejection/graft sclerosis. (**a**) Artery with severe luminal narrowing due to a combination of acute (intimal arteritis) and active chronic cell-mediated allograft rejection. The latter appears as two 'cushion-like' areas of intimal fibrosis with mononuclear inflammation. (**b**) Stage II of chronic rejection/graft sclerosis characterized by septal and acinar fibrosis that extends to the center of the acinar lobules

Table 7 Urological complications after pancreas transplant

Urinary tract infection	39–58%
Hematuria	11–26%
Graft pancreatitis	19–26%
Duodenal leaks	7–17%
Urethral complications (urethritis, disruptions)	2–3%
Calculi	2.5–5%

posttransplant. Causes of hematuria include anastomotic bleeding (suture or staple line), duodenitis, urinary tract infection (UTI), postbiopsy, cytomegalovirus infection, reflux pancreatitis, rejection, bladder calculi, and pseudoaneurysm (Esterl et al. 1995; Polo et al. 2009). Treatment for the review etiologies includes Foley catheterization, bladder irrigation, clot evacuation, cystoscopy with fulguration of duodeno-vesical anastomosis, and surgery (Gettman et al. 1996).

Graft pancreatitis after bladder-drained pancreas transplant presents with diffuse abdominal pain, graft tenderness, nausea, vomiting, and irritative voiding. Lab results reveal hyperamylasemia and sometimes concurrent urinary tract infections. Preoperative urodynamic evaluation may show detrusor areflexia or hyperreflexia. Abdominal ultrasound or computerized tomography is diagnostic in majority of cases. Treatment includes Foley catheterization, bowel rest, intravenous fluids, and antibiotics for concurrent urinary tract infections, if present. Enteric drainage conversion is recommended in patients with severe or recurrent episodes of reflux pancreatitis (Gettman et al. 1996).

Duodenal leak presents similarly to graft pancreatitis with abdominal pain and graft tenderness. Early leaks are mainly due to technical reasons or ischemia and can be small and asymptomatic. Late duodenal leaks are a result of ulceration, CMV infection, or chronic inflammation (Polo et al. 2009). CT scan and cystoscopy in bladder-drained cases are used to diagnose a duodenal leak. Small asymptomatic leaks can be treated with Foley catheterization, while leaks which present with peritonitis are managed with exploratory laparotomy.

Urethral complications are presumably related to drainage of exocrine pancreatic secretions through the bladder. The patient usually presents with irritative voiding symptoms, penile pain, and perineal discomfort. Urethritis usually resolves after short-term Foley catheterization. Calculus formation can also occur in the bladder-drained pancreas allograft. Nonabsorbable sutures or a surgical staple can act as a nidus within the bladder for calculus formation (Polo et al. 2009). Patient with bladder drainage sometimes have to take oral sodium bicarbonate to prevent chronic metabolic acidosis (intractable) secondary to exocrine pancreatic secretions (Figs. 10, 11, and 12).

Cystoenteric conversion rate is reported between 6% and 23% (Stephanian et al. 1992; Kleespies 2011). Major indications for conversion include chronic urinary tract infection, recurrent

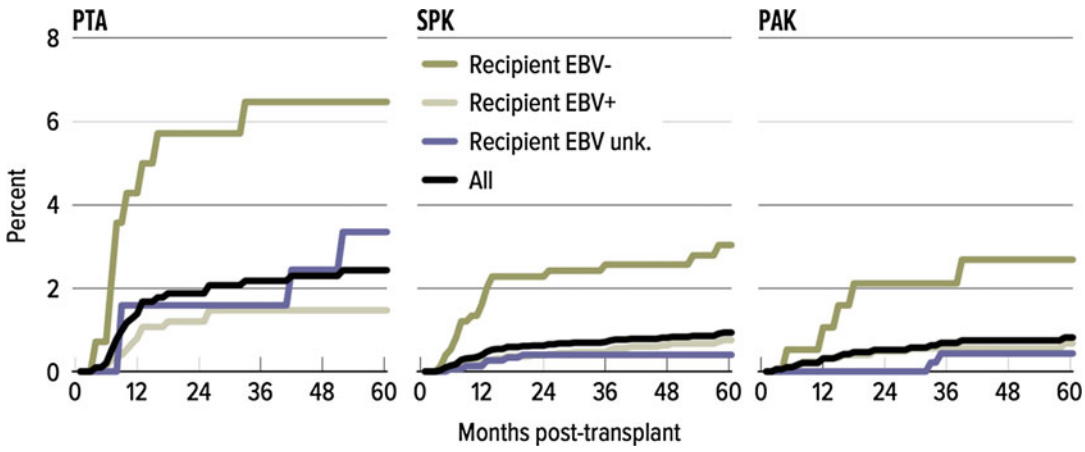

Fig. 10 Incidence of PTLD (posttransplant lymphoproliferative disorder) among adult pancreas transplant recipients 2006–2010, by recipient Epstein-Barr virus (EBV) status

Fig. 11 WHO classification of PTLD (posttransplant lymphoproliferative disorder

Category	Subtype
Early lesions	Reactive plasmacytic hyperplasia
Polymorphic PTLD	Polyclonal Monoclonal
Monomorphic PTLD	B-cell lymphomas Diffuse large B-cell lymphoma Burkitt's/Burkitt's-like lymphoma Plasma cell myeloma T-cell lymphomas Peripheral T-cell lymphoma Rare types (gamma/delta, T/natural killer cell) Other types Hodgkin's disease-like Plasmacytoma-like

reflux pancreatitis, chronic intractable metabolic acidosis, and urethritis. Complications related to enteric drainage conversion include anastomotic leak, pancreatitis, duodenal perforation, and intraabdominal infection. One important risk factor is the development of rejection after enteric-drainage conversion, which can lead to graft loss in almost 15% of recipients (Jimenez-Romero et al. 2009). Some authors have recommended waiting at least 1 year after the last rejection episode before converting to enteric drainage; however, other series have not shown any difference in rejection episodes after conversion (Jimenez-Romero et al. 2009).

Enteric drainage and bladder drainage pancreas transplants have similar patient and graft survival (Gruessner et al. 2011). The rate of enteric drainage has significantly increased, and more than 80% of pancreas transplant recipients now have enteric drainage versus bladder drainage as shown in Fig. 12.

Miscellaneous

The incidence of pancreatic pseudocyst formation is reported to be less than 10% but is difficult to determine, as not every pancreatic fluid collection

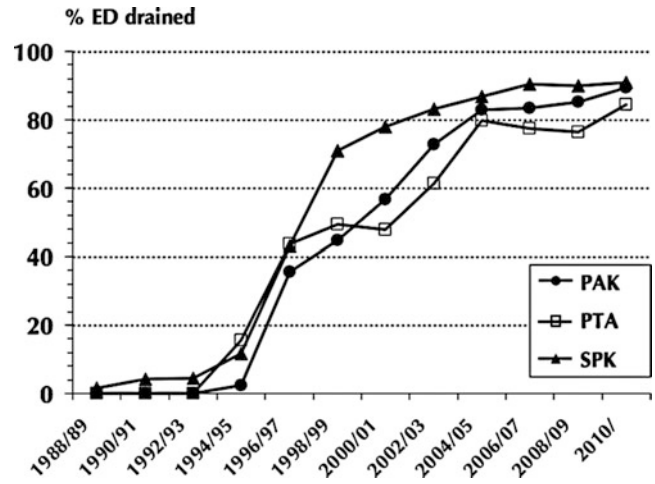

Fig. 12 Rate of enteric drainage in pancreas transplantation in the USA, 1988–2010. *ED* enteric drainage (Gruessner et al. 2011)

is a true pseudocyst. The diagnosis can be made by ultrasound, CT scan, or MRI. If imaging studies are equivocal (e.g., in the case of a complex pseudocyst with multiple septations and an inhomogeneous appearance), a pseudocyst can be differentiated by amylase levels in the aspirate. All symptomatic and large asymptomatic peripancreatic fluid collections should be drained. More aggressive treatment is indicated from the outset in the case of complications, namely hemorrhage, cyst perforation, or a symptomatic pseudocyst that is refractory to repetitive nonoperative intervention. For bladder- and enteric-drained grafts, internal drainage may involve creating a cyst jejunostomy. A cyst cystostomy can be performed in the case of a bladder-drained pancreas. Graft pancreatectomy in these cases should rarely be employed except in unusual circumstances such as complicated pseudocysts that do not respond to the nonoperative and operative treatment outlined above, in particular complicated pseudocysts with infection or major hemorrhage due to erosion into large pancreatic or peripancreatic blood vessels.

Conclusion

Careful selection of donor and recipient, meticulous surgical technique, and high clinical suspicion can prevent and decrease surgical complications.

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Donor Evaluation and Procurement

Muhammad Irfan Saeed

Contents

Abstract

Organ procurement is the first and an important step in the process of solid organ transplantation. There is a significant shortage of transplantable organs, e.g., kidneys, livers, pancreas, hearts, lungs and intestines, with waitlist time increasing annually. It is important to collaborate with other providers involved in the process of organ procurement to maximize the deceased donor organ pool. Careful donor evaluation and organized procurement processes can help increase the deceased organ donation pool.

Keywords

Brain death · Donor · Procurement · Recovery · Preservation · Machine perfusion

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Introduction

Organ procurement can be divided into three phases:

Phase 1: From declaration of death to procurement
Phase 2: Intraoperative management
Phase 3: Organ preservation

Phase 1

Concept of Death

In 1963, the first organ recovery was performed from a brain dead donor. Until this time, there was no legal definition for death. In 1968, an ad hoc committee of the Harvard Medical School deliberated on the definition of brain death and published its report (Ad Hoc Committee of the Harvard Medical School 2008). The committee described the following characteristics of a permanently nonfunctioning brain, a condition it referred to as "irreversible coma" or brain death:

1. Unreceptivity and unresponsitivity: patient shows total unawareness to external stimuli and unresponsiveness to painful stimuli.
2. No movements or breathing: all spontaneous muscular movement, spontaneous respiration, and response to stimuli are absent.
3. No reflexes: fixed, dilated pupils (pupillary response to light), lack of eye movement even when touched (corneal reflexes), or lack of eye movement when turned (oculocephalic reflex – doll's eye phenomenon); placing ice water in the ear (oculovestibular reflex – caloric response); lack of response to noxious stimuli; and unelicitable tendon reflexes (Guidelines for the Determination of Death 1981).

In addition to these criteria, a flat electroencephalogram (EEG) was recommended. The committee also noted that drug intoxication and hypothermia, which can both cause reversible loss of brain function, should be excluded as causes. The report was used in determining patient care issues and candidacy for organ transplantation.

The condition of irreversible coma, or brain death, needs to be distinguished from the persistent vegetative state, in which patients manifest cycles of sleep and wakefulness.

Clinically, an apnea test is performed in addition to the above mentioned tests to declare brain death (Benzel et al. 1992). Sometimes confirmatory tests are performed to declare brain death – but sometimes used to shorten the observation period (hemodynamic instability) or when there may be concern for potentially reversible metabolic conditions.

1. Cerebral Blood Flow Studies (CT angiography, radionuclide angiography, transcranial Doppler ultrasound)
2. Electroencephalography (EEG)
3. Brainstem auditory evoked potentials (BAERs) (Table 1)

How to Approach the Donor Family Obtaining Consent for Organ Donation

After the patient is declared brain dead and it is determined that the family is interested in organ donation, the next step is approaching the deceased donor's family to obtain consent.

The relationship between the local organ procurement organization (OPO) and hospital is the basic foundation for cadaveric donation (Guadagnoli et al. 2003; Simpkin et al. 2009; Tarino et al. 2012). A referral call to the OPO will initiate the process. Early referral after death is important to quickly evaluate the suitability of the deceased patient for organ donation.

It is highly recommended that one avoid the topic of organ donation while explaining to the family that the patient has expired (Klintmalm and Levy 1999). One should also avoid medical jargon while explaining the circumstances leading to the patient's death. As the deceased donor family is going through much stress and grief, highly trained OPO personnel should approach the family or next of kin. It is also important to train

Table 1 Legislative history of organ procurement/transplant in the USA (Jafar 2009)

Year	Law	Description
1968	Uniform Anatomical Gift Act	An individual could irrevocably donate upon death his or her organs for medical purposes by signing a single document before witnesses
1972	Social security Amendments	Medicare coverage extended to dialysis and kidney transplant to most persons < 65 years of age with chronic kidney disease
1978	The Uniform Brian Death Act	This model law established that irreversible cessation of all brain functioning, including brain stem, is death
1980	The Uniform Determination of Death Act	Replaced Uniform Brain Death Act (which did not address traditional criteria for determining brain death). This Act defines death when an individual sustains either 1. Irreversible cessation of circulatory or respiratory function, or 2. Irreversible cessation of all functions of brain or brain stem function
1984	National Organ Transplant Act (NOTA)	United States Department of Health and Human Services established a regulated system of nonprofit Organ Procurement and Transplantation Network to acquire all usable organs from potential donors and allocate equitably among transplant candidates using medical criteria. Organ commerce was prohibited under NOTA
1986	Omnibus Budget Reconciliation Act	Mandated all hospitals participating in Medicare and Medicaid programs to increase the donor pool
1991	Patient Self-Determination Act	Seeks to ensure physicians' awareness of organ donation through patient's instructions and use of advance directives, free living wills, and power of attorney for organ transplant
1999	Organ Donor Leave Act	Entitled 30 days of paid leave to organ donor
2004	Organ Donation and Recovery Improvement Act	Directs Department of Health and Human Services to grant awards to states, transplant centers, qualified organ procurement organizations, other entities for transplant related travel, and subsistence expenses incurred by individuals
2006	Uniform Anatomical Gift Act – revised	Expanded the list of people who could make an anatomical gift on behalf of the deceased in the event that no determination has been made before death. It also encouraged the use of life support systems at or near death for the purpose of maximizing procurement of organs medically suitable for transplant
2007	Charlie W. Norwood Living Organ Donation Act	Willingly related or unrelated donors who are biologically incompatible with their intended recipients agree to donate an organ to an unknown recipient. In exchange, their intended recipient either receives an organ (paired exchange) or a higher position on the waitlist (list donation)
2008	The Stephanie Tubbs-Jones Gift of Life Medal Act	Establishes the Stephanie Tubbs-Jones Gift of Life Medal for organ donors and their families
2013	HIV Organ Policy Equity (HOPE) Act	Allows research and transplantation of HIV positive organs into HIV positive patients. Federal Law previously prohibited it

hospital medical personnel such as ICU attendings, nurses, and residents about approaching possible donor families. Sensitivity to different religions, traditions, and grief processes gives comfort to the donor family and helps them in making a decision. The patient's family should be educated regarding donation after brain death (DBD) or donation after cardiac death (DCD)

(Bellingham et al. 2011). Allowing the family space and time to process the information usually affects the donation process positively.

Who Should Take the Consent for Donation?

The medical team taking care of the patient plays a significant role in the donation process by setting the groundwork. Usually, separating discussions about donation and death helps to increase the donation rate (Klintmalm and Levy 1999). Additionally, higher consent rates are achieved when OPO personnel approach the patient's family. Family members should be approached away from public areas. Explaining the donation process to the family and answering questions will alleviate anxiety. Explaining consent in the family's native language will also help them understand quickly and easily. Even if the family declines consent, it is important to treat the family with respect and dignity.

Medical Management of Organ Donor

Body systems go through significant physiological changes after brain death (e.g., autonomic, cardiovascular, endocrine, etc.). Monitoring lines are required for donor management. Organ-specific laboratory and radiological studies are ordered (Table 2).

Besides the above mentioned general recommendations, there are other medical issues which should be addressed. Hyperkalemia (>5.5 mEq/L) can cause delayed AV conduction, prolonged PR interval, and a widening QRS complex. If severe, it can cause sinus bradycardia and sinus arrest or cardiac standstill. Standard measures should be taken to correct hyperkalemia. Hypokalemia (<3.5 mEq/L) should be addressed as it can lead to ventricular irritability and atrial tachycardia. Potassium replacement should be given peripherally as central line administration can precipitate hyperkalemic cardiac arrest.

Management of hypothermia is also critical as it can delay the diagnosis of brain death (Klintmalm and Levy 1999). The brain-dead patient cannot compensate for heat losses (inability to shiver and failure to vasoconstrict). Adverse effects of hypothermia include myocardial depression, decreased oxygen delivery to organs (left shift of organ dissociation curve), coagulopathy, and fluid losses. Treatment of hypothermia includes covering exposed surfaces, use of warm blankets (Bear hugger) and heat humidifier to the anesthesia circuit, warming of administered fluids, and raising room temperature.

Monitoring donors in the ICU is an integral part of their management. Placement of an arterial line (A-line), central venous pressure line (CVP), 12-lead electrocardiogram (EKG), and Swan-ganz catheter (if 2D-ECHO ejection fraction less than 40%) is warranted Klintmalm and Levy 1999. Mixed venous oxygen saturation (target of $\geq$ 60%) and serial serum lactate levels should be obtained.

There are also organ-specific recommendations for organ procurement (Table 3).

Whenever possible, the donor's medical history is obtained from his/her next of kin and a battery of serological testing is performed to determine any potential infectious transmission from donor to recipient (Kovacs et al. 2014). These tests include:

1. Hepatitis B surface antigen (HBsAg), hepatitis B core antibody total, and IgM (anti-HBc total, anti-HBc IgM).
2. Hepatitis C antibody (HCVAb)
3. HIV 1 and 2 antibodies
4. Syphilis (nontreponemal tests)
5. Epstein-Barr virus (EBV): IgM and IgG antibodies
6. Cytomegalovirus (CMV): IgM and IgG antibodies
7. ULTRIO HIV
8. ULTRIO hepatitis C virus and hepatitis B virus

Phase 2

After organs are accepted by transplant centers, the OPO coordinator sets up the procurement in collaboration with the respective teams. The procurement team usually includes one to multiple

Table 2 Donor management recommendations (Shemie et al. 2006)

Medical condition	Recommendation
HTN related to intracranial pressure	Thresholds to initiate therapy 1. SBP > 160 mmHg and/or 2. Mean arterial pressure > 90 mmHg Preferred treatment 1. Nitroprusside, 0.5–5 mcg/kg per minute and/or 2. Esmolol, 100–500 mcg/kg bolus followed by 100–300 mg/kg/min infusion Infusions must be titrated until desired effect is achieved. Alternative agents used are nitroglycerin and/or labetalol (prolonged biological life 4–6 h)
Hemodynamic instability	1. Fluid resuscitation 2. First line vasopressor agent: vasopressin (0.04 unit/min) 3. Second line vasopressor agents: norepinephrine, epinephrine, phenylephrine (dose should be titrated to achieve clinical effects, with no predetermined upper limits) 4. Dopamine
Diabetes insipidus (DI)	Defined as urine output > 4 mL/kg/h 1. Associated with rising sodium levels > 145 mmoL/L 2. Associated with rising serum osmolality (>300 mOsm) and decreasing urine osmolality (<200 mOsm) Dose of DDAVP for diabetes insipidus 1. Adult: 1–4 mcg IV then 1–2 mcg IV every 6 h to achieve urine output < 4 mL/kg/h 2. Pediatric: 0.25–1 mcg IV every 6 h to achieve urine output < 4 mL/kg/h Vasopressin can also be used alone or along with DDAVP. If patient is hemodynamically unstable, then first choice is vasopressin
Hypernatremia	Defined as serum sodium level > 155 mmoL/L 1. It is independently associated with postdonation hepatic dysfunction or graft loss 2. In addition to sodium control, calcium, phosphate, potassium, and magnesium levels should be empirically normalized
Hormonal therapy (combined) – thyroid hormone, vasopressin, and methylprednisolone	Defined as administration of 1. Thyroid hormone (T3 or T4), 20 mcg IV bolus followed by 10 mcg/h IV infusion 2. Vasopressin, 1 unit IV bolus followed by 2.4 units/h IV infusion 3. Methylprednisolone, 15 mg/kg IV every 24 h 4. Combined hormonal therapy should be given in all donors with EF less than 40% on 2 D ECHO or if patient is hemodynamic instable
Transfusion thresholds	1. Target hemoglobin of 9–10 g/dL is most appropriate to optimize cardiopulmonary function in face of hemodynamic instability, while hemoglobin of 7 g/dL is the minimum acceptable limit for stable donors 2. There are no defined targets for platelet concentration, INR, or PTT. Transfusion is indicated for clinical bleeding 3. Blood draws for donor serology and tissue typing should occur before transfusions to minimize the risk of false results related to hemodilution
Infectious work up	1. An initial baseline blood culture, urine culture, and endotracheal tube aspirate should be carried out for all donors repeated after 24 h and as needed 2. Positive blood cultures or confirmed infections are not a contraindication to organ donation 3. Antibiotic therapy should be initiated in cases of proven or presumed infections. Duration of therapy depends upon virulence of the organism, and decisions should be made in consultation with the transplant team and infectious diseases service 4. No minimum duration of antibiotic therapy before organ procurement is defined at this time
Broad spectrum antibiotics	1. Empiric broad spectrum antibiotics are not indicated during ICU care of the organ donor 2. Decisions regarding use of perioperative antibiotics should be at the discretion of the surgical team
Glycemic control	1. Serum blood glucose goal 70–140 mg/dL, with insulin infusion if needed 2. Use of insulin should not be misinterpreted as a form of insulin dependence that might preclude organ donation. Hemoglobin A1C should be measured under these circumstances

(*continued*)

Table 2 (continued)

Medical condition	Recommendation
Nutrition	1. Intravenous (IV) dextrose infusions should be given routinely 2. Routine enteral feeding should be initiated or continued as tolerated and discontinued on call to the operating room 3. Parenteral nutrition should not be initiated; however, where it has been initiated, it should be continued

Abbreviations: *SBP* Systolic blood pressure, *ECHO* Echocardiography, *DDAVP* 1-desamino-D-arginine vasopressin, *INR* International normalized ratio, *PTT* Partial thromboplastin time, *ICU* Intensive care unit

surgeons, a perfusionist, a surgical assistant, and a coordinator. Donation can be after brain death (DBD) or after cardiac death (DCD).

The most important procedure in the donor operation is to cross clamp; the steps of cross clamp are:

1. Tying off the distal aorta (above bifurcation)
2. Placement of cannula in distal aorta below renal arteries
3. Access supraceliac aorta to place a vascular clamp
4. Cutting inferior vena cava (IVC) through the opened pericardium

There are two different ways to perform the brain dead donor surgery:

Warm dissection – when most of the dissection is performed before cross clamping

Cold dissection – when most of the dissection is performed after cross clamping

In the case of DCD donors, dissection is always performed in cold. After cross clamping, cold preservative solution is flushed through the organs and ice is placed externally on all the transplantable organs. The organs are then procured separately or en bloc, depending on the surgeon's preference and skill. Special attention is paid to the vascular anatomy and possible anomalies, such as identifying a replaced/accessory right hepatic artery from the superior mesenteric artery (SMA) or a replaced/accessory left hepatic artery from the left gastric artery (Fig. 1, Tables 4 and 5).

In the case of kidney procurement, careful assessment is required to identify the origin of the renal artery or arteries. Ureteral injury and renal vein injury can easily occur if attention is not paid.

Intraoperative surgeon assessment of the pancreas for fibrosis, edema, and fat is the most important predictive factor of outcomes following pancreas transplantation (Axelrod et al. 2010).

Surgical Standards Specifically Related to Pancreas Organ Recovery (Khwaja – ASTS Academic Universe)

1. The root of the small bowel mesentery should be stapled (or vessels individually ligated) at least 3 cm away from the head of the pancreas and uncinate process to avoid injury to the inferior pancreaticoduodenal arcade. Umbilical tapes and other forms of mass ligation should be avoided.
2. The portal vein should be divided halfway between the pancreas and liver (mid-hilar level) or at least 1 cm above the superior pancreatic border (Table 6).
3. The splenic artery should not be dissected into the substance of the pancreas, as this may result in injury to its dorsal pancreatic branch. After division close to its celiac origin, the splenic artery should be tagged with a fine prolene suture. The splenic artery runs a tortuous course along the upper pancreatic border and one must therefore proceed with caution when dissecting in this region.
4. The superior mesenteric artery (SMA) does not need to be procured with an aortic cuff. If there is a replaced/accessory right hepatic artery, this can be traced to its SMA origin by kocherizing the duodenum and dissecting

Table 3 Organ-specific recommendations (Shemie et al. 2006)

Organ	Recommendations
Heart	1. 2D ECHO 2. Serum troponin levels (troponin I and troponin T) 3. Coronary angiography Male > 55 years or female > 60 years of age Male > 40 years or female > 45 years of age in the presence of two risk factors Presence of three or more risk factor at any age History of cocaine use Cardiovascular risk factors include smoking, hypertension, diabetes, hyperlipidemia, body mass index > 32, family history, prior history of coronary artery disease, ischemia on EKG, anterolateral regional wall motion abnormalities on ECHO, and ejection fraction (EF) ≤ 40% on 2D ECHO
Lungs	Mechanical ventilation with the following targets: 1. Fraction of inspired oxygen (FiO2) titrated to keep oxygenation saturation ≥ 95% and partial pressure of arterial oxygen (PaO2) ≥ 80 mm of Hg 2. pH: 7.35–7.45; PaCO2: 35–45 mm of Hg 3. Positive end expiratory pressure (PEEP): 5 cm H_2O 4. Partial pressure of arterial oxygen/fraction of inspired oxygen (P/F) ratio > 300 5. Tidal volume: 8–10 mL/kg 6. Peak inspiratory pressure ≤ 30 cm of H_2O Bronchoscopy can be performed at the donor hospital and results can be relayed to transplant surgeon Antimicrobial therapy should be based on the results of Gram stain or culture or suspected/confirmed bronchopneumonia Monitoring continuous pulse oximetry, serial arterial blood gas, endotracheal tube suctioning, chest radiography, bronchoscopy, and broncho-alveolar lavage Corticosteroid therapy is currently indicated as the immune-modulating therapy for potential lung donors, although protocols of administration are not uniform
Liver	Potential liver donors are assessed for: 1. History of jaundice, hepatitis, excessive alcohol ingestion 2. Liver enzymes (AST, ALT), bilirubin (direct/Indirect), INR, or PT, repeated every 6 h 3. Hepatitis panel: hepatitis B (surface antigen, surface antibody, core antibody), hepatitis C virus antibody 4. Liver biopsy is recommended in ICU before procurement in consideration with liver transplant team for: Body weight > 100 kg or body mass index > 30 or HCVAb positive Distant procurement: when procurement team is not readily available If the liver biopsy cannot be performed in the ICU and indications for biopsy exist, the liver should still be offered. The procurement team can perform an intraoperative liver biopsy and assess whether the liver is suitable for transplant at their center
Kidneys	Potential kidney donors are assessed for: 1. History of hypertension, diabetes mellitus, and smoking 2. Urinalysis 3. Serum creatinine/blood urea nitrogen (BUN) are measured every 6 h 4. Use Cockroft-Gault equation for measurement of creatinine clearance 5. Kidney biopsy (performed postprocurement) Age > 65 years or a younger age with history of any of the following: Hypertension Diabetes mellitus Serum creatinine > 1.5
Pancreas	1. Donor hyperglycemia is not a contraindication to transplant 2. Check hemoglobin A1C 3. Prolonged hypotension in donor in association with high-dose vasopressors is a relative contraindication

Abbreviation: *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *HCVAb* hepatitis C virus antibody

it free from the undersurface of the pancreas. The SMA is then divided just distal to the origin of the right hepatic artery, preserving an adequate length with the pancreas. Rarely, the accessory hepatic artery will course through the substance of the pancreas and the pancreas will have to be sacrificed in favor of the liver. Other variations in arterial

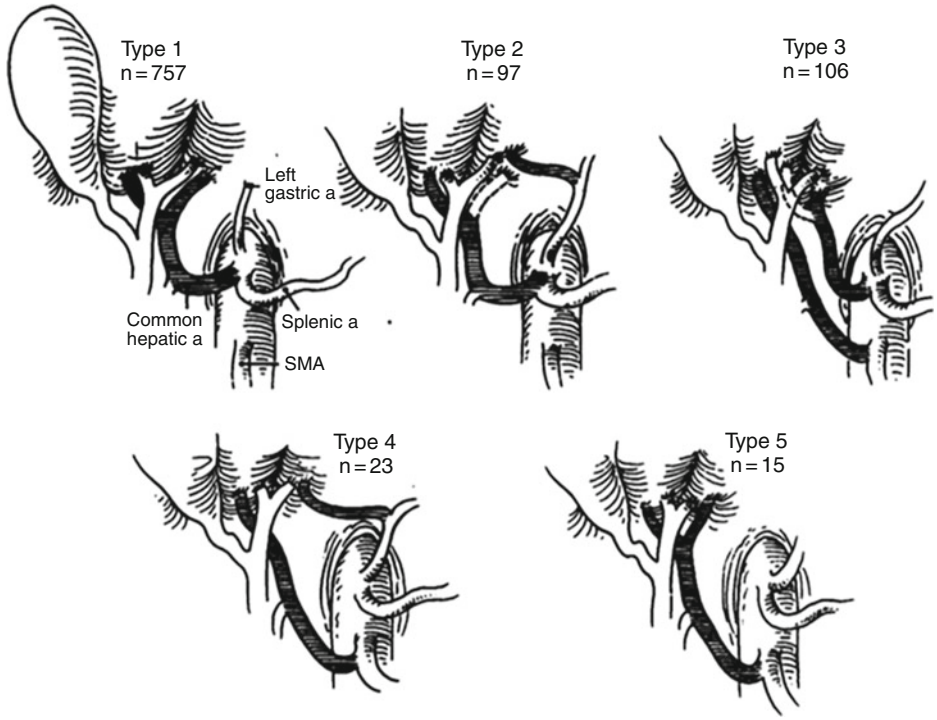

Fig. 1 Classification of hepatic arterial types (Hiatt et al. 1993)

supply include a common celiac-SMA trunk and a direct aortic origin of the splenic artery, and these should not affect either liver or pancreas retrieval. If the liver is not being procured for transplant, then the celiac and SMA are kept on a common aortic cuff, the common hepatic and gastric vessels ligated, thus maintaining all the pancreatic blood supply and obviating the need for subsequent reconstruction.

5. The duodenum is flushed via a nasogastric tube, prior to cross-clamping, with an antibiotic and antifungal solution. The duodenum is stapled above or just below the pylorus and at the 4th portion or proximal jejunal level.
6. The common bile duct, gastroduodenal artery (GDA), and inferior mesenteric vein (IMV) should be ligated or tagged. Some recipient surgeons use the GDA for arterial reconstruction, in which case, it should be carefully isolated and tagged.
7. The spleen should not be separated from the pancreas and the splenic hilum left intact as the splenic vessels and tail of the pancreas can be easily damaged.
8. Avoid pushing IMV catheters for portal flush all the way into the pancreas as this may damage the splenic vein. The SMV may be cannulated, as long as the venotomy is made well away from the pancreas and distal to the subsequent mesenteric staple line. Some centers prefer to limit the aortic flush coursing through the pancreas to 1–2 L, and this should be ascertained beforehand. Vessel loops placed on the SMA and splenic artery allow for control of aortic flush. Either University of Wisconsin (UW) or HTK solutions may be used. However, there are reports of higher rates of acute rejection, graft pancreatitis, and even worse graft survival with HTK.
9. In cases involving concomitant small bowel procurement, the SMA should be transected well-distal to the origin of the inferior pancreaticoduodenal arcade. The exact site of transaction should be agreed upon by the

Table 4 Hepatic artery vasculature types (Hiatt et al. 1993)

	Classifications of hepatic arterial types		
	Type	Description	Percent
Michels[3] (n = 200)	1	Normal	55
	2	Replaced LHA from LGA	10
	5	Accessory LHA	8
			18
	3	Replaced RHA from SMA	11
	6	Accessory RHA	7
			18
	4	Replaced RHA + LHA	1
	7	Accessory RHA + LHA	1
	8	Replaced RHA + accessory LHA or replaced LHA + accessory RHA	2
			4
	9	CHA from SMA	2.5
	10	CHA from LGA	0.5
Current series (n = 1,000)	1	Normal	75.7
	2	Replaced or accessory LHA	9.7
	3	Replaced or accessory RHA	10.6
	4	Replaced or accessory RHA + replaced or accessory LHA	2.3
	5	CHA from SMA	1.5
	6	CHA from aorta	0.2

LHA left hepatic artery, *LGA* left gastric artery, *RHA* right hepatic artery, *SMA* superior mesenteric artery, *CHA* common hepatic artery

pancreatic and intestinal surgeon and is generally distal to the origin of the middle colic artery. The distal stumps of the SMA and SMV should be carefully controlled and oversewn or tagged with a fine prolene suture. There are no anatomic circumstances that should preclude recovery of both the small intestine and pancreas. If the liver and intestine are being procured for a combined transplant, it is not possible to preserve the whole pancreas for a separate transplant.

10. Full length of an iliac artery (all of the common, with as much length of external and internal) should be procured for "Y-graft" construction. Care should be taken to avoid traction injury to the iliac bifurcation. A segment of iliac vein should also be kept with the pancreatic graft in case portal vein extension is needed. It is preferable to avoid vessels that contained indwelling catheters (Fig. 2).

Iliac vessels (artery and vein) are also procured and shared between liver and pancreas teams. For liver transplants, the iliac vessels may be used as aortic conduit if the native hepatic arteries are dissected as to maximize arterial inflow. In pancreas transplantation, the iliac arteries are required for back table construction of a Y-graft connection between the splenic artery and SMA so that a single anastomosis is performed in the recipient. Vein grafts may also be used for portal vein jump grafts in liver transplants and extension grafts in pancreas transplant when portal vein is short (ASTS Academic Universe).

Table 5 Hepatic artery types – collected series (Hiatt et al. 1993)

Hepatic arterial types (%) – collected series							
Type	Current series (n = 1000)	Michels[3] (n = 200)	Rong[4] (n = 120)	Kemeny[5] (n = 100)	Rygaard[4] (n = 216)	Daly[7] (n = 200)	Niederhuber[8] (n = 111)
1	75.7	55	51	59[a]	75.5	76	73[b]
2	9.7	18	12	17	4.6	7.7	10
3	10.6	18	21	18	13.4	12	11
4	2.3	4		2	1.9		2
5	1.5	2.5	5	3	1.4		
Other	0.2	0.5	11	1	3.2	6	5

[a]Trifurcation: 9%
[b]Trifurcation: 14%

Table 6 CT scan findings overall and by gender among 1,957 potential kidney donors at the Mayo clinic between 2000 and 2008

CT findings of the kidneys and renal arteries	Overall, *n* (% [95% CI])	Men, *n* (%)	Women, *n* (%)	*P*	
				Unadjusted	Age-adjusted
n	1,957	827	1,130		
Renal artery variants	565 (29[27,31])	266 (32)	299 (27)	0.0060	0.0062
>1 left renal artery	528 (27 [25,29])	238 (29)	290 (26)	0.12	0.12
>1 right renal artery	528 (27 [25,29])	238 (29)	290 (26)	0.12	0.12
>1 renal artery on either side	845 (43 [41,45])	384 (46)	461 (41)	0.013	0.013
>1 renal artery on both sides	248 (13 [11,14])	120 (15)	128 (11)	0.037	0.037
Renal artery abnormalities					
Fibromuscular dysplasia	54 (2.8 [2.1,3.6])	10 (1.2)	44 (3.9)	0.0007	0.0015
Other renal artery narrowing or atherosclerosis	103 (5.3 [4.3,6.4])	48 (5.8)	55 (4.9)	0.36	0.080
Renal artery dilatation	12 (0.6 [0.3,1.1])	5 (0.6)	7 (0.6)	0.97	0.96
Parenchymal abnormalities					
Medullary sponge kidney	40 (2.0 [1.5,2.8])	13 (1.6)	27 (2.4)	0.2101	0.24
Focal scarring	70 (3.6 [2.8,4.5])	15 (1.8)	55 (4.9)	0.0006	0.0011
Diffuse thinning or atrophy of either kidney	17 (0.9 [0.5, 1.4])	2 (0.2)	15 (1.3)	0.023	0.023
Parenchymal calcification	21 (1.1 [0.7,1.6])	13 (1.6)	8 (0.7)	0.074	0.058
Indeterminate mass	27 (1.4 [0.9,2.01])	11 (1.3)	16 (1.4)	0.87	0.97
Polycystic kidney disease	6 (0.3 [0.1,0.7])	2 (0.2)	4 (0.4)	0.66	0.61
Other parenchymal abnormality	2 (0.1 [0.0, 0.4])	1 (0.1)	1 (0.1)	0.83	0.70
Kidney stones	210 (11 [9.4,12])	87 (11)	123 (11)	0.80	0.84
Upper urinary tract dilatation	49 (2.5 [1.9,3.3])	7 (0.9)	42 (3.7)	0.0002	0.0002
Any congenital abnormality	26 (1.3 [0.9,1.9])	8 (1.0)	18 (1.6)	0.22	0.20
Solitary or horseshoe or pelvic kidney	4 (0.2 [0.1,0.5])	1 (0.1)	3 (0.3)	0.47	0.51
Malrotation of either kidney	14 (0.7 [0.4,1.2])	4 (0.5)	10 (0.9)	0.31	0.27
Congenital lobulation	9 (0.5 [0.2,0.9])	3 (0.4)	6 (0.5)	0.59	0.56

95% CI, 95% confidence interval

Phase 3

The most common method of organ preservation is cold storage. The organs are stored in preservative solution at a temperature of 0–4° C. Cooling the organs from 37 °C to 4 °C slows the enzymatic reactions by tenfold or more (Fuller 1991). Hypothermia is the most critical component of successful preservation. During warm ischemia, the lack of oxygen and perfusion leads to a very rapid decrease in the availability of energy (ATP) derived from mitochondrial and glycolytic catalyzed reactions. Without ATP, the tissue loses control of its intracellular environment, resulting in changes in cytosolic ionic composition (protons, Ca^{2++}, K^{+}, Na^{+}), activation of hydrolytic enzymes (phospholipases, proteases, endonucleases), and destruction in the stability of the intracellular structural components (microtubules, cytoskeleton membranes). Hypothermia may be effective by blocking the activities of various hydrolytic enzymes. This has been shown to increase the tolerance of organs, tissues, and cells to ischemia (Imberti et al. 1993). Clearly,

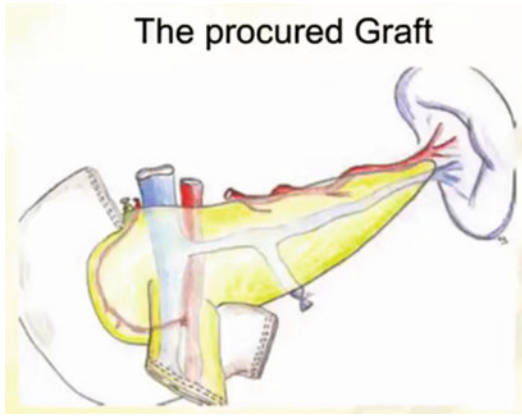

Fig. 2 Cadaveric pancreas graft

enzymatic reactions continue at 0–4 °C, as is evident by the accumulation of end products of metabolism (lactate, glucose, purine nucleotides, etc.) in cold-stored tissues. It is likely that continued metabolic activity leads to ischemia reperfusion injury when organs are rewarmed and reperfused.

Besides hypothermia, there are other important interventions that include the presence of impermeable molecules, which remain outside the cell preventing them from swelling in cold storage. The use of antioxidants in organ preservation is a common approach to improve posttransplant results. There are numerous studies demonstrating that warm and cold ischemia/perfusion leads to rapid formation of oxygen free radicals (OFR) (Bulkley and Morris 1990; Lemasters et al. 1995; Land and Messmer 1996). Glutathione is used in preservative solutions to enhance antioxidant activity. Furthermore, allopurinol blocks the activity of xanthine oxidase, which has been proposed to be a major source of superoxide anions during reperfusion of organs (Kurose and Granger 1995). The mode of action of glutathione is not clear but may be related to inhibition of proteases or reduction of lipid peroxidation stimulated by OFR generation (Ferguson et al. 1991, 1993). Mitochondria are highly dependent upon glutathione for suppression of oxidative injury.

A key factor in organ preservation may be the rate of regeneration of ATP upon reperfusion. This requires leaving the mitochondria intact during preservation and reperfusion, as well as supplying the cells with precursors for ATP regeneration. In UW solution, adenosine was added to elevate the concentrations of these ATP precursors and provide substrates of ATP regeneration (Southard and Belzer 1993).

Controversy exists over the solution content of sodium and potassium. Most successful preservation solutions are the intracellular-type solutions with high concentrations of potassium. Solutions such as Collins, EuroCollins, Marshall's, and UW all contain high concentrations of potassium. The benefit of these highly concentrated solutions is debated, as several investigators and studies have shown that electrolyte content may not be important and can be reversed (high Na^+ or K^+) (Moen et al. 1989; Howden et al. 1992).

Another controversy in cold storage solution composition is related to the need for a colloid (e.g., hydroxyethyl starch) in cold storage solution. Colloids counteract the hydrostatic pressure in continuous machine perfusion of organs. In cold storage, however, the organs are not exposed to hydrostatic pressure except during the initial flush. Hydroxyethyl starch has recently been shown to suppress proteolysis during cold storage in rat livers. Organs are better preserved with colloid solution, thus UW solution is a preferred solution as it contains colloid (hydroxyethyl starch) (Table 7).

Hypothermic Machine Perfusion

Hypothermic machine perfusion was developed by Belzer et al. and is used in several centers across the USA and around the world. Hypothermic machine perfusion can be continuous or pulsatile. This technology was created in order to maintain organs for donation viable for longer periods of time. There is a significant shortage of organs, especially kidneys, as more than 120,000 people are waiting for a kidney transplant in the USA alone (OPTN). In contrast to the growing volume of organ transplant waitlists, there has not been any significant increase in deceased organ donation according to the 2012 SRTR (Scientific

Table 7 Composition of UW solution (Viaspan – Summary of product characteristics)

Substance	Concentration	Function
Lactobionic acid (as lactone)	105 mmol/L	Impermeant, suppression of hypothermic swelling
Potassium dihydrogen phosphate	25 mmol/L	pH buffer, maintenance of intracellular Na^+/K^+ concentration, restoration of high energy phosphate (ATP)
Magnesium sulfate	5 mmol/L	Preservation of intracellular magnesium concentration
Raffinose	30 mmol/L	Impermeant, suppression of hypothermic swelling
Adenosine	5 mmol/L	Restoration of high energy phosphate (ATP)
Glutathione	3 mmol/L	Antioxidant, restoration of high energy phosphate (ATP)
Insulin	100 units/L	Promotion of anaerobic energy production
Dexamethasone	8 mg/L	Cytoprotective
Allopurinol	1 mmol/L	Inhibition of xanthine oxidase activity and purine metabolism/ reduction of oxygen free radicals
Hydroxyethyl starch	50 g/L	Colloid, reduction of interstitial edema and endothelial cell swelling
Sodium hydroxide 40%	27 mmol/L	Maintenance of intracellular Na^+/K^+ concentration
Potassium hydroxide 56%	100 mmol/L	Maintenance of intracellular Na^+/K^+ concentration
Penicillin G	200,000 units	Bactericidal

Registry of Transplant Recipients) annual report (SRTR) (US Scientific Registry 2012). According to this report, the discard rate for kidneys with KDPI (kidney donor profile Index) > 85% is more than 40% and is almost 20% for KDPI between 35% and 85% (SRTR).

As of December 4, 2014, the kidney allocation system has changed, leading to more donor kidneys being shipped across procurement organization boundary lines. Presumably, this will add to increased cold ischemia times; it is yet to be determined what impact, if any, this will have on patient and graft survival in kidney transplant recipients.

Organ Recovery Systems® (Itasca, IL, USA) has developed a kidney preserving and transport machine known as LifePort® kidney transporter (version 1.0 and latest version 1.1).This perfusion pump is a portable, insulated transporter with ultrasonic bubble detection, on board GPS, USB port (for data transfer), enhanced display, and 24-h operation capability. Kidneys are perfused with Belzer's machine perfusion solution available as Kidney Preservation Solution-1® (KPS-1) at temperatures of 1–8 °C. Systolic perfusion pressure is set at 30 mm of Hg, and kidney flow (ml/min), resistance (mmHg/ml/min), and temperature of ice and trap (in Celsius) are continuously recorded. Donor kidneys are usually flushed with UW solution in situ and then placed on perfusion pumps until transplantation (Fig. 3).

Hypothermic machine perfusion of kidneys reduces the risk of delayed graft function (DGF) and also improves 1-year kidney graft outcomes (Moers 2009, 2012). Delayed graft function in kidneys from donation after cardiac death (DCD) is almost 40%, and machine perfusion reduces the risk of DGF in those kidneys as well (Southard and Belzer 1993; Snoeijs et al. 2006; Jochmanns 2010; Plata-Munoz et al. 2010). DGF increases the cost of a renal transplant and impacts outcomes of graft survival. Reducing DGF and increasing graft survival ultimately lowers the costs associated with kidney transplantation (Buchanan et al. 2008; Garfield et al. 2009).

Machine perfusion not only maintains a high ATP content but also removes end products of metabolism that could accumulate to toxic concentrations in tissues. Machine perfusion allows control of cellular pH and can continuously deliver substrates and cytoprotective agents like antioxidants, enzyme inhibitors, and precursors for cytoprotective agents (Klintmalm and Levy 1999).

Fig. 3 LifePort® kidney transport pump

Organ Recovery Systems® has also developed the subnormothermic perfusion pump for liver transport based on the concept of the kidney perfusion pump. It is in the investigational stage of development and is not available for commercial sale. The first series of successful liver transplants employing hypothermic machine perfusion was published in 2010. It demonstrated that machine-perfused livers tend to have less early allograft dysfunction than those preserved by cold storage (5% vs. 25%, $p = 0.08$) (Guarrera 2010). Hypothermic liver perfusion may increase the organ pool and improve graft outcomes in the future. Additionally, heart, lung, pancreas, and multiorgan (i.e., liver and kidneys) transport perfusion pumps are currently in development.

Donor Organ Risk Index

In order to project graft survival rates, donor organ risk indices have been developed for the kidney, liver, and pancreas. Parameters used to calculate are organ specific (Table 8).

These risk indices should not be used as the sole tool to assess the organ for transplantation; a complete medical history, laboratory results, radiological studies, and intraoperative assessment should be included to finalize the decision, ultimately keeping in mind the needs of the organ recipient.

Table 8 Donor organ risk index

Kidney donor profile index (KDPI) (Merion et al. 2005; Rao et al. 2009)	Liver donor risk index (LDRI) (Feng et al. 2006)	Pancreas donor risk index (PDRI) (Axelrod et al. 2010)
Age	Age	Age
Height	Height	Height (cm)
Weight	Ethnicity/race	Gender
Ethnicity/race	Location: donor hospital	Body mass index (BMI)
Cause of death	Cause of death	Cause of death – CVA or Non-CVA
History of hypertension	Donor meets DCD criteria	Height
History of diabetes mellitus	Cold ischemia time (hr)	Donor meets DCD criteria
Serum creatinine	Partial liver	Cold ischemia time (hr)
Hepatitis virus C status		Creatinine (mg/dL)
Donor meets DCD criteria		Pancreas after kidney status

Conclusion

Organ procurement is a complex process, which requires patience, organization, coordination, and expertise. At a time when families have lost their loved ones, the gift of organ donation can save the lives of many sick people, allowing them to become a healthy part of the community.

The most important issue surrounding organ donation is how to expand it. Community education is extremely important to clarify misconceptions related to death and organ transplantation (Rodrigue 2006a). Financial assistance with organ donation is a controversial debate, while organ trafficking is a global problem that cannot be condoned or tolerated (Rodrigue 2006b; Jafar 2009). Cultural sensitivity should be practiced when educating minority communities about organ donation (Saleem et al. 2009; Rady and

Verheijde 2013). Opportunities for individuals to express their will to donate should be expanded (e.g., driver's license renewal, voter registration, passport registration, online donor registry, living will, or marriage certificate) (Salim et al. 2010; Rodrigue et al. 2014). Simplifying the consent process may improve donation rates, and some suggest adopting the Spanish model in which everyone is considered an organ donor unless they opt out (Prottas and Batten 1988; Mossialos et al. 2008). New innovations in donor management, organ allocation, and preservation will increase the availability of usable organs from the existing organ pool (Wood 1996; Smith et al. 2012; Novitzky et al. 2014; Dupuis et al. 2014; Callahan et al. 2014; Schold et al. 2005; Treckmann et al. 2011; Mgbako et al. 2013; Woien et al. 2006).

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Follow-Up Care of the Pancreas Transplant Recipient

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Abstract

Although the management of pancreas transplant recipients shares some similarities with those of other solid organ transplants, the complexities of pancreas transplantation merit a particular knowledge base. This chapter describes the major points of posttransplant medical management of pancreas recipients. Attention is devoted to the idiosyncrasies of management as it pertains to the surgical technique utilized in graft implantation. Surveillance of pancreatic graft function through evaluation of endocrine and exocrine parameters vis-à-vis renal function is also discussed. Other topics include evaluation and management of posttransplant diabetes, hypertension, hyperlipidemia, anemia, and posttransplant malignancies. Finally, attention is devoted to the topic of pregnancy after transplantation.

Keywords

Transplantation · Pancreas · Kidney · Diabetes · Pregnancy · Rejection · Infection · Immunosuppression · Amylase · Hypertension · Hyperlipidemia · Acidosis · Electrolyte · Calcium · Malignancy

Introduction

Despite improvements in the establishment of normoglycemia in patients with type I diabetes through the use of automated devices, which provide exogenous insulin administration and glucose monitoring, pancreas transplantation remains the only definitive long-term treatment for patients with insulin-dependent diabetes mellitus (Rainer Gruessner 2004). Notwithstanding the long-term benefits of pancreas transplantation, aggressive medical management of diabetes type 1, as advocated by data from the Diabetes Control and Complications Trial (DCCT), in conjunction with improved insulin delivery systems has changed the paradigm for referral for transplantation. The unintended consequence of this shift in practice pattern is that many patients referred for transplantation have often had as much as 15–20 years of active diabetes. This prolonged exposure to the disease may result in systemic sequelae which may render potential candidates high risk or medically ineligible for transplantation. Furthermore, those patients listed for transplantation are increasingly of higher complexity, given factors such as increasing age, body mass index (BMI), or degree of anti-HLA antibody sensitization. The combination of incident transplant cohort with increasing complexity and a prevalent transplanted cohort of increasing size and vintage poses special challenges to clinicians charged with the care of these patients. This chapter will address the idiosyncrasies of the medical management of the pancreas transplant patient in a succinct and logical manner based on the current medical evidence and standard of care.

Surgical Technique as a Consideration in the Medical Management of Pancreas Transplants

The surgical technique utilized in the management of pancreatic endocrine and exocrine secretions are of upmost importance in the recipient's subsequent medical follow-up. As noted in previous chapters, management of exocrine pancreatic secretions in transplant recipients is usually accomplished by one of two techniques: either drainage of the duodenal segment to the bladder (bladder drainage) (BD) or to the small bowel (enteric drainage) (ED). Bladder drainage has two main advantages. First, it enables the timely diagnosis and treatment of rejection via the ability to measure urine amylase levels. Second, bladder drainage avoids the bacterial contamination and peritonitis which may occur with enteric drainage leaks. Such leaks, in the setting of profound immunosuppression, are associated with considerable morbidity and mortality.

The utilization of bladder drainage is also associated with unique metabolic and urologic derangements. Many patients experience metabolic acidosis secondary to bicarbonate loss in the urine, volume depletion, recurrent urinary tract infections, dysuria, recurrent hematuria, and recurrent episodes of graft pancreatitis secondary to reflux of urine into the ductal system of the graft and late duodenal leaks (Gruessner and Gruessner 2013). Complications from BD may require the surgical conversion of a BD to an ED. The conversion rate from BD to ED

has been reported between 10% and 35% (West et al. 1998). The most common reasons are: difficult to correct metabolic acidosis due to excessive sodium bicarbonate loss, recurrent urinary tract infections, recurrent pancreatitis, duodenal perforations at the anastomosis site leading to late leaks, and urologic complications.

ED is a good alternative to BD for drainage of pancreatic graft exocrine function as it poses a more physiologic method of managing these secretions. Both techniques have the similar patient and graft survival. The introduction of lymphocyte depleting agents in immunosuppression induction, allowing for a decreased reliance in the use of high dose steroids, along with the advancement of surgical techniques has enabled routine use of ED, whereas now ED is being used in the majority of transplants. In 2010, ED was used in 91% of SPK, 89% of PAK, and 85% of PTA patients (Gruessner 2011).

In terms of the endocrine drainage of the pancreas, it has long been hypothesized that portal venous drainage of pancreas allografts should offer physiologic benefits and has been advocated to be superior to systemic venous drainage. The prevention of hyperinsulinemia and improvements in the lipoprotein profiles in patients receiving portal-drained pancreas allografts have been documented in small case series. Although portal drainage may be superior to systemic drainage in ameliorating metabolic complications, the former is associated with a higher rate of allograft thrombosis (Hakim 2010). Currently, in the enteric-drained transplants, systemic venous drainage is performed in the majority of cases. In 2010, portal drainage accounted for only 18% in SPK and PAK and for 10% in PTA (Gruessner 2011). In practical terms, the difference in either of these techniques is clinically insignificant as far as posttransplant follow-up is concerned.

Monitoring of Pancreas Graft Function

Monitoring Exocrine Function: Amylase

A BD pancreas offers a simple and noninvasive method of assessing graft function and timely diagnosis of rejection. Exocrine pancreas may precede dysfunction of the endocrine pancreas by 5–7 days. In BD, amylase levels are measured routinely in the recipient urine and serum. There is no "normal" urine amylase level; however, observing a trend of decreasing levels is concerning. The finding of an increasing serum amylase with concomitant decreasing urine amylase, despite normal glucose levels, is a highly sensitive albeit poorly specific marker for a rejecting pancreas allograft. Hence, amylase is an early marker heralding rejection, whereas glucose is a late marker; however, this presentation may also be seen in other more benign conditions, such as in non-immune-mediated graft pancreatitis. In this setting, a broad differential diagnosis needs to be considered.

Figure 1 provides an example of a patient which presented with an acute rise in serum amylase with a concomitant decrease in urine amylase. Early testing showed significant urinary retention and the presumptive diagnosis of reflux pancreatitis was made. With the placement of an indwelling Foley catheter, appropriate bladder decompression was achieved and prompt normalization of both the serum and urinary amylase promptly followed.

In cases where there is no obvious etiology for a rising serum amylase in the face of a declining urinary amylase, prompt investigation is warranted as to rule out a diagnosis of allograft rejection. If appropriate treatment for rejection is swiftly implemented while the patient remains normoglycemic, there is a good chance to salvage the graft. More than 90% of pancreas rejection episodes are reversible in the absence of hyperglycemia. Once serum hyperglycemia is detected, it is associated with a low probability of reversal of rejection (Gruessner and Gruessner 2013).

Monitoring Endocrine Function

The ultimate goal of pancreas transplantation is the achievement of euglycemia and ultimately insulin independence, particularly in those patients with type I diabetes. Notwithstanding the fact that exocrine abnormalities usually precede endocrine dysfunction, evaluation of glucose metabolism is an integral component in patient management. In patients with an ED graft, clinicians are unable to monitor urine amylase as a

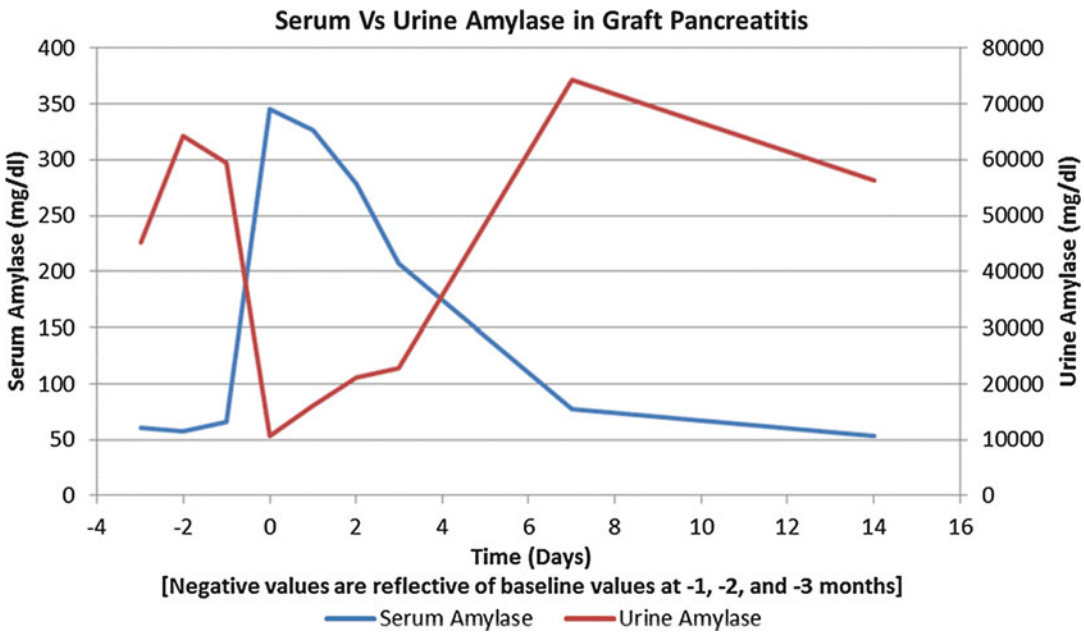

Fig. 1 Graft pancreatitis in a BD SPK patient presenting with urinary retention. Amylase promptly returned to baseline after bladder decompression with an indwelling urinary catheter

surrogate marker of function, yet as part of the standard panel of lab tests, glucose and hemoglobin A1c (HbA1c) are routinely obtained. Laboratory abnormalities (fasting glucose $>$ 100 mg/dL or HbA1c $>$ 6.0) usually prompt further investigation of glucose metabolism.

First Phase Insulin Response

Insulin is released from the pancreas in a biphasic manner in response to a square-wave increase in arterial glucose concentration. The first phase consists of a brief spike in serum insulin concentrations in which levels increase rapidly to a peak at 2–4 min followed by a decrease to a nadir at 10–15 min. This is followed by the second phase, in which levels gradually increase progressively to a pseudo-steady state over 2–3 h.

The first phase response provides an accurate assessment of β-cell function. The square-wave increase in arterial glucose concentration can be achieved via intravenous administration of either glucose or glucagon; the former being more commonly performed. In one method, a 25 g intravenous bolus of dextrose is given and insulin levels are drawn at times −5, 0, 2, 5, 10, and 30 min. A ratio is then formulated. Basal insulin level (time −5 min) is subtracted from subsequent values and insulin levels at 2 and 5 min are summed and divided by the 10 and 30 min total. Ratios less than 1.4 are associated with pancreatic dysfunction and graft loss (Henry et al. 1994). Figure 2 shows an example of an appropriate first phase insulin response with a ratio of 2.79.

Alternate Methods of Endocrine Function Assessment

An alternate method consists in measuring the second phase insulin response. Currently the oral glucose tolerance test (OGTT) is commonly used. Two hours after administering a 75 g oral glucose load, patients are considered to have impaired glucose tolerance (IGT) if plasma glucose is between 140 and 200 mg/dL. Values greater than 200 mg/dL are diagnostic for diabetes. Oral glucose tolerance results have been associated with long-term outcomes of pancreatic graft function after successful pancreas-kidney transplantation.

Other methods which have shown effectiveness in evaluating insulin sensitivity are the homeostasis model assessment of insulin

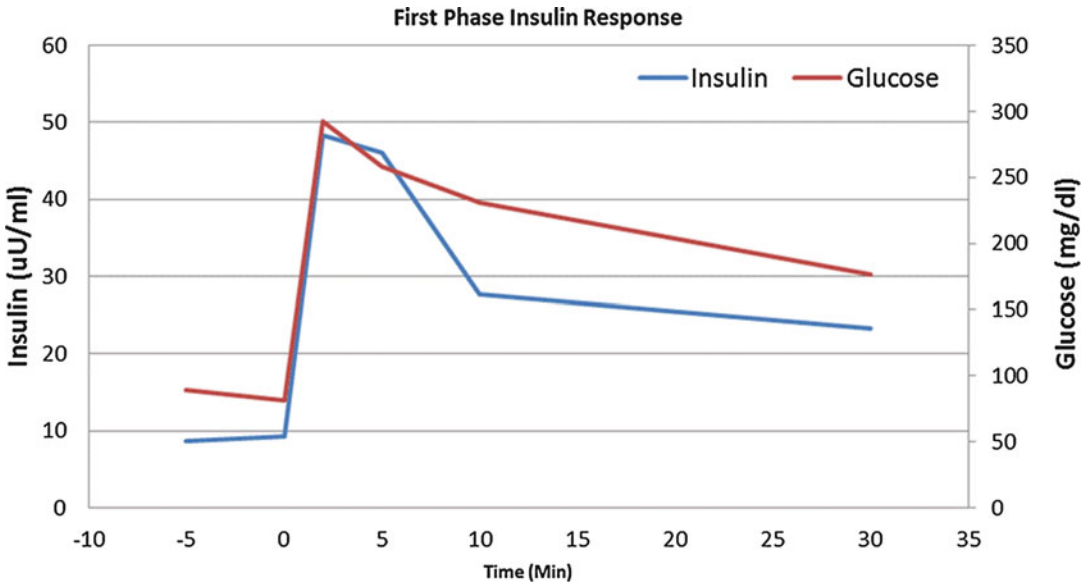

Fig. 2 Normal first phase insulin response in a SPK patient after a 25 g IV glucose bolus

sensitivity (HOMA-IS) and quantitative insulin sensitivity check index (QUICKI). HOMA estimates steady state beta cell function and insulin sensitivity, as percentages of a normal reference population. QUICKI is similar to HOMA as both utilize identical variables, but QUICKI uses a different mathematical manipulation in its formula which increases the ability to predict insulin sensitivity. In practice, measurement of the first phase insulin response provides a better assessment of the transplanted graft function as it does not take into account other metabolic derangements, such as peripheral resistance to insulin.

Monitoring for Rejection

Indirect Diagnosis of Pancreas Rejection: Serum Creatinine

In patients with a simultaneous pancreas and kidney transplant both allografts originate from the same donor and are hence immunologically identical. This provides a distinct advantage in the diagnosis of allograft rejection. In these cases, approximately 90% of pancreas rejection episodes are preceded by or occur in conjunction with a rejection of the transplanted kidney (Gruessner and Gruessner 2013). As such, renal dysfunction as exhibited by elevated serum creatinine levels can be used as an early marker for pancreas rejection given that serum creatinine may show alterations even in the absence of changes in amylase and glucose levels. Albeit highly sensitive, elevation of serum creatinine in a SPK is not specific for rejection and a full evaluation has to be performed before resorting to a biopsy. As compared to performing a biopsy of the pancreas, a renal biopsy is technically simpler and safer and has a higher success rate for obtaining clinically useful tissue for diagnosis; however, it is not without risks.

In evaluating a patient with an unexplained rise in the serum creatinine, clinicians most commonly consider these differential diagnosis and workup (Table 1).

Most etiologies for elevations of creatinine may be elucidated clinically; reserving a biopsy for those cases in which the diagnosis is equivocal through noninvasive methods.

Most clinicians would agree that evidence of rejection on a transplant biopsy is sine qua non for its diagnosis and subsequent treatment. Despite advances in genomics and biomarkers, a biopsy remains the gold standard test for the diagnosis of

Table 1 Differential diagnosis, etiology, and workup for rising creatinine in a SPK patient

Potential diagnosis	Specific etiologies	Diagnostic testing
Structural abnormalities	Stenosis in transplant renal artery/vein Hydronephrosis (Stenosis in transplant ureter) Fluid collections (Seroma/urinoma/hematoma)	Renal ultrasound with Doppler
Calcineurin inhibitor toxicity	Supratherapeutic levels of cyclosporine or tacrolimus	Acute toxicity: serum drug levels Chronic toxicity: biopsy
Chronic allograft changes interstitial fibrosis/tubular atrophy	Insidious worsening of renal function due to nonspecific chronic injury to a transplant graft	Clinical history Confirmatory: biopsy
Common renal etiologies	Identical to those of a native kidney: prerenal (volume depletion in BD), intrarenal, and postrenal (poor bladder emptying in autonomic dysfunction)	Clinical history Testing as appropriate
Renal allograft rejection	Multifactorial recipient cellular and or humoral immunological response to transplanted allograft antigens	Clinical history Gold standard: biopsy
Infections	Systemic: sepsis leading to AKI Local: pyelonephritis Opportunistic: CMV, BK, EBV	Clinical history Microbiological cultures Serum PCR viral loads

rejection. For a clinician, a biopsy provides not only the diagnosis per se but also the mechanism (cellular and/or humoral), chronicity (acute vs. chronic), and severity when utilizing a standardized classification, such as the Banff criteria. This information is vital to the clinician in determining the best regimen to follow in treating the underlying process.

Immunological Monitoring

Antibody-mediated rejection (AMR) of the pancreas was described in 2006; subsequently, other reports have validated these findings (Melcher et al. 2006). Anti-HLA antibodies play a central role in the development of AMR. In nonpancreas allografts, recipients with preformed donor-specific antibodies (DSA) at the time of transplantation and those who subsequently develop them de novo after transplantation have both been shown to have poorer graft outcomes (Mao et al. 2007). Most studies on the effect of anti-HLA antibodies in pancreas recipients are single center reports, yet data seem to underscore the importance of DSA in the pancreas allograft. DSA has been shown to develop in approximately 14–16% of recipients and has been shown to be a strong independent predictor of pancreas graft failure. This effect seems to be more pronounced in isolated pancreas transplants as opposed to SPK (Mittal et al. 2014).

Routine measurement of anti-HLA antibodies in all pancreas transplant patients is controversial. With the introduction of single antigen solid phase testing platforms, it is possible to identify the presence of specific antibodies and to quantify its amount; however, lack of standardization in laboratory methodology impedes making direct comparisons between centers. Additionally, most studies have analyzed the development of DSA in a retrospective manner; there is not enough data to recommend routine prospective analysis of anti-HLA antibodies in all recipients. More importantly, if de novo DSA is identified in the absence of graft dysfunction, there is little consensus on the appropriate management. For these reasons, the practice of obtaining routine HLA measurements is at this time a center-specific decision.

Direct Diagnosis of Pancreas Rejection

Biopsy

When noninvasive testing is not able to elucidate the etiology of graft dysfunction, a diagnostic

tissue biopsy is most often the next step in management. There are various approaches to obtaining a tissue diagnosis. A commonly utilized technique, regardless of the graft being BD or ED, is via a percutaneous approach using ultrasound or CT guidance. The complication rate for this procedure ranges between 3% and 11%. A commonly seen abnormality is elevated serum amylase, which can occur in up to 29% of cases. This enzyme elevation is usually short lived and resolves within 3 days (Margreiter et al. 2013). Complications described in this approach include intraabdominal hemorrhage, macro hematuria, allograft pancreatitis, exocrine leak, and damage to other organs. Historically, other approaches have been described in the literature. In the case of a bladder-drained pancreas, a cystoscopy-directed needle biopsy of the transplanted graft duodenum has been described. Likewise, the use of an endoscopic approach to obtain a sample of the transplanted duodenum has also been described in a BD. An open biopsy ultimately provides the best visualization of the graft but also is the most invasive procedure.

Once adequate tissue is obtained, it is submitted to pathology for analysis. When considering a pancreas allograft biopsy, the samples should be sent to a pathologist experienced in the processing and interpretation of these samples. A detailed discussion on pancreas histology and pathology can be found elsewhere in this text.

Acid/Base and Electrolyte Dysfunctions

Metabolic Acidosis

Given the urinary loss of bicarbonate from pancreatic exocrine secretions, acid base disturbances, primarily hyperchloremic metabolic acidosis (HCMA), are not uncommon in BD. HCMA, by definition, refers to the presence of metabolic acidosis that is due to the deficit of sodium bicarbonate; it is simply a descriptive term based on an observed associated rise in the plasma chloride. Nevertheless, there is no primary role for chloride in the pathogenesis of metabolic acidosis. Pancreatic exocrine secretions may be as high as 3 L per day with bicarbonate concentrations reaching up to 150 mmol/L, hence it is not surprising to frequently see HCMA in BD (Bro-Rasmussen et al. 1956). In normal physiological conditions, patients with metabolic acidosis exhibit acute compensations of the pH via the development of respiratory alkalosis until renal compensatory mechanisms can take over. The kidney will gradually increase distal tubule ammonium excretion in the setting of increased proximal tubular bicarbonate reabsorption. Despite physiological compensatory mechanisms, over two third of patients will require treatment for HCMA (as defined by a serum HCO_3 $<$20 meq/L). Most patients receive oral $NaHCO_3$ supplementation in the form of oral tablets or a "bicarbonate cocktail" solution. The colloquial term "bicarbonate cocktail" describes a solution prepared with half a teaspoon of household baking soda dissolved in four ounces of water containing a powered soft drink (e.g., Kool-Aid) and/or common "household" sugar. For comparison, a 650 mg NaHCo3 contains 7.6 meq of Na. Half a teaspoon of baking soda contains 26.8 meq or approximately 3.5 tablets of NaHCO3.

In those patients unresponsive to oral therapy, intravenous $NaHCO_3$ or even acetazolamide has been utilized successfully (Ketel et al. 1992). Although seemingly paradoxical, carbonic anhydrase inhibitors have been shown to reduce the volume of pancreatic secretions and hence bicarbonate loss in a bladder-drained pancreas, hence its effectiveness.

Volume Depletion

In BD, pancreatic exocrine secretions are not just a significant source of bicarbonate loss but also sodium. This sodium loss leads to volume depletion, resulting in renal dysfunction, electrolyte disturbances, and in severe cases hemodynamic instability.

Hyperkalemia and worsening metabolic acidosis are associated with volume depletion. Renal dysfunction [prerenal acute kidney injury (AKI)] results from the kidney's inability to maintain adequate intraglomerular pressure through autoregulatory mechanisms. In the setting of calcineurin inhibitors (CNI), such as cyclosporin

(CSA) and tacrolimus (TAC), there is worsened afferent arteriole vasoconstriction and decreased ability for renal autoregulation. The consequence of this decrease in intraglomerular pressure is a diminished glomerular filtration rate (GFR) with subsequent drops in the filtrate volume and flow rates. These changes result in decreased delivery of sodium to the distal tubule disrupting the intraluminal electronegative gradient needed for distal tubular hydrogen and potassium ion secretion, which coupled with an existing underlying bicarbonate loss leads to systemic hyperkalemia and worsening metabolic acidosis (Taal et al. 2012). Additionally, CNIs cause suppression of plasma renin activity and a tubular insensitivity to aldosterone, both of which may impair potassium excretion.

When faced with cases of prerenal AKI in the setting of metabolic acidosis, intravenous volume expansion with bicarbonate-containing solutions is the first step in management. Clinicians normally opt for solutions containing 75 meq of $NaHCO_3$ mixed in a 0.45% NaCl 1 L bag or 150 meq of $NaHCO_3$ mixed in a 5% dextrose 1 L bag depending on the degree of metabolic acidosis or volume depletion.

As an interesting note, when assessing volume status the diagnosis is often clinical based on physical examination alone. When orthostatic (positional) hypotension is noted, it must be interpreted cautiously given that preexisting autonomic dysfunction may render equivocal results. There is no utility in calculating a fractional excretion of sodium (FENa) in BD as a means of determining volume depletion in the diagnosis of prerenal AKI. Given the constitutive pancreatic exocrine sodium loss in BD, calculation of FENa will render equivocal results.

Immunosuppression

The optimal selection and management of immunosuppression is a contentious topic of discussion. Given the potential complications and narrow therapeutic index of most immunosuppressive agents, close and frequent monitoring of serum drug levels is a key component of posttransplant surveillance. This topic is covered in depth in a separate chapter of this text.

Glucose Level Abnormalities

Hyperglycemia

Posttransplant diabetes mellitus (PTDM) and impaired glucose tolerance (IGT) have been recognized as complications of solid organ transplantation. The development of diabetes after transplantation has serious consequences for the patient, being associated not just with reduced graft function and increased risk of graft loss but also patient survival (Kasiske et al. 2003). The goal of pancreas transplantation is to achieve euglycemia in the setting of an insulin-free regimen, hence ultimately preventing worsening of long-term diabetic complications. The development of hyperglycemia after transplantation is an alarming complication which needs to be fully evaluated.

Most centers utilize the World Health Organization definitions in diagnosing IGT and PTDM. The methods for monitoring glucose metabolism in the transplanted pancreas have been detailed above. Patients with a fasting plasma glucose (FPG) value of 126 mg/dL or above are defined as having PTDM; those with values between 110 and 125 mg/dL are defined as having impaired fasting glucose (IFG). When the oral glucose tolerance test (OGTT) is used, a 2-h plasma glucose of between 140 and 199 mg/dL is diagnostic of IGT, whereas values above 200 mg/dL are diagnostic of PTDM.

Reported incidences of PTDM vary depending on choice of maintenance immunosuppression regimen and study design. One large single center study followed 674 pancreas transplant recipients over a 10-year period, with mean follow-up of more than 6 years. The described incidence of PTDM was 14% and 25% at 3 and 10 years after transplant, respectively (Neidlinger et al. 2010). The etiology of PTDM is divided into early versus late causes. Early causes are seen in the perioperative period and may be due to technical complications, vascular thrombosis, delayed or primary nonfunction, acute pancreatitis, acute rejection,

infections, and drug toxicities. Late causes are associated with acute or chronic rejection, chronic pancreatitis, recurrence of autoimmunity, chronic drug toxicities, and weight gain post transplantation.

Late causes are usually due to two broad etiologies: decreased production of insulin by the transplanted graft or peripheral resistance to insulin. An abrupt decrease in insulin production is most often seen with acute allograft rejection or recurrent autoimmune β-cell destruction, whereas an insidious decreased insulin production is often related to graft sclerosis. The histopathological findings in each are described elsewhere in this text. Often the etiology for PTDM is secondary to a combination of both decreased graft function and increased peripheral insulin resistance.

Immunosuppressive medications have been associated with the development of PTDM. Corticosteroids in particular have long been recognized as causing impaired blood serum glucose control given its role in inducing peripheral insulin resistance. The use of CNIs is also associated with an increased risk of developing PTDM, with evidence suggesting that TAC is more diabetogenic than CSA, particularly in high-risk patients. Other risk factors include weight gain posttransplant, race, ethnicity, family history, higher BMI, allograft donor age, hepatitis C, and CMV infection (Neidlinger et al. 2010).

PTDM is managed similar to diabetes in the general population. Current guidelines for treating of PTDM differentiate the treatment depending on early versus late diagnosis. In the peritransplant period, the recommendation is for early use of insulin. In late PTDM, consensus guidelines recommend initiation with lifestyle modification followed by oral antidiabetic therapy using insulin as a last resort (Sharif et al. 2014). Metformin is generally avoided given the potential for renal dysfunction in this patient population. Insulin sensitizers such as thiazolinediones may decrease metabolic demand on the β-cell and has been shown to be safe in managing PTDM in nondiabetic liver and renal transplant patient. Secretagogues such as sulfonylureas or meglitinides can improve insulin secretion from the pancreas graft, although these agents may not preserve β-cell function over time. Agents that increase the glucagon-like-peptide-1 (GLP1), such as GLP-1 analogues and dipeptidyl peptidase-IV inhibitors, may show promise in preserving the remaining beta cell function by preventing apoptosis and promoting β-cell growth in the pancreas graft. In islet cell transplant recipients, GLP-1 analogues have been shown to stimulate insulin secretion, hence potentially reducing exogenous insulin administration in some patients and delaying the need to resume insulin in others. There are currently no data on the use of sodium/glucose cotransporter 2 (SGLT2) inhibitors in transplant patients. This new class of medications has been approved to treat patients with type 2 diabetes mellitus and a GFR of >45 mL/min to lower blood glucose. SGLT2 inhibitors target most of the sodium glucose cotransport in the proximal tubule decreasing renal tubular glucose reabsorption producing subsequent glycosuria. As one of the main adverse effects of these medications is increases in urinary tract infections, their use is not recommended in the (immunosuppressed) transplant population. Ultimately, insulin may be needed in many patients. Management and dosing is similar to that of the nontransplant population.

It must be noted that a posttransplant patient who resumes insulin is not automatically classified as a pancreas graft loss. Determination of a definition for when a pancreas graft failure occurs has been equivocal and contentious. Proposed definitions include the moment when the recipient undergoes a pancreatectomy, re-registers for a repeat pancreas transplant, or registers for an islet transplant after receiving a pancreas transplant. Other definitions proposed include the moment when a recipient's insulin use is greater than or equal to 0.5 units/kg/day for a consecutive 90 days or when fasting C-peptide production falls under a certain threshold. Finally, the date of a recipient's death has also been proposed as an unequivocal event (OPTN 2015). As of yet there is no official definition.

Hypertension

Hypertension may be seen in up to 60% of SPK recipients; however, this represents a 15–30%

reduction from the pretransplant prevalence with some data, suggesting that patients with bladder-drained pancreas have a more marked decreased incidence of hypertension as opposed to enteric-drained recipients (Hricik et al. 2000). The incidence appears to be highest in the peritransplant period and then decreases over the subsequent 12 months. Pretransplant hypertension and the use of cyclosporine are most commonly associated with posttransplant hypertension. The goal blood pressure is based on extrapolations from JNC VII and KDOQI guidelines which recommend a target blood pressure < 130/80 mmHg and in cases where proteinuria is present <125/75 mmHg (Bakris et al. 2000).

Similar to the nontransplanted population, the first-line treatment for hypertension is lifestyle modification. When lifestyle modifications are insufficient, medications are introduced. Calcium channel blockers (CCB) are often used (dihydropyridine are preferred to nondihydropyridine, as they do not interact with the CYP3A4 pathway) to treat hypertension. Additional medications include diuretics (being mindful of volume status); angiotensin-converting enzyme inhibitors (ACE-I); and angiotensin receptor blockers (ARB) (being mindful of hyperkalemia and decreased GFR when used in combination with a calcineurin inhibitor). Beta blockers are used cautiously as they may blunt hypoglycemic unawareness. Unless there is a compelling indication, most clinicians avoid certain medications such as: those can lead to orthostasis (alpha blockers), centrally acting agents (clonidine), or direct vasodilators (hydralazine, minoxidil) as pancreas recipients often have a blunted autonomic response and are prone to orthostatic hypotension.

Hyperlipidemia

Given the alterations of lipid metabolism in the diabetic patient, it is not surprising to note there is improvement in the overall lipid profile posttransplantation as defined by decreased total cholesterol (TC) and postprandial triglyceride (TG) levels and increased high-density lipoprotein (HDL) cholesterol (Hakim 2010). However, derangements of lipid metabolism remain a common occurrence. There are various risk factors implicated in hyperlipidemia: choice of immunosuppressive regimen, age, diet, rapid weight gain, hyperinsulinemia, preexisting hypercholesterolemia, allograft dysfunction, proteinuria, and the use of blockers and diuretics (Pham et al. 2007).

Different immunosuppressive drugs exhibit particular lipid derangement profiles. Steroids have been associated with inducing peripheral resistance to insulin and interfering with enzymatic pathways resulting in increased levels of very low density lipoprotein (VLDL), TC, and TG. Cyclosporine has been associated with increased TC and low density lipoprotein (LDL) levels with little effect on HDL. Tacrolimus has an attenuated effect on TC and LDL as compared to cyclosporine despite also being a calcineurin inhibitor. Sustained improvements in TC and LDL have been shown in patients who have been switched from cyclosporine to tacrolimus. In patients with SPK, this effect does not appear to be affected by the method of pancreatic exocrine secretion drainage. Both everolimus and sirolimus have been shown to increase total cholesterol and triglyceride levels in a dose-dependent manner with no distinct differences between both agents. Lipid derangements can be seen as early as 2 weeks after initiation of mTOR inhibitors and improvement within 4 weeks after discontinuation.

The definition and treatment of hyperlipidemia are derived from the ATP III guidelines and adapted to the posttransplant population (Kasiske et al. 2004). A fasting lipid panel (FLP) should be checked within the first 6 months posttransplant and at a minimum annually after the first year posttransplant. Goal FLP parameters are TG <200, LDL <100, and non-HDL <130. The first-line treatment of hyperlipidemia consists of lifestyle modification for 3 months. If this intervention is ineffective, medications are introduced. Statins, fibrates, and niacin are the most commonly used agents (Fig. 3).

Statins are generally safe and efficacious in transplant recipients when clinicians are aware of potential drug interactions, particularly in the case of calcineurin inhibitors. Statins can be metabolized by the CYP450-3A4 pathway

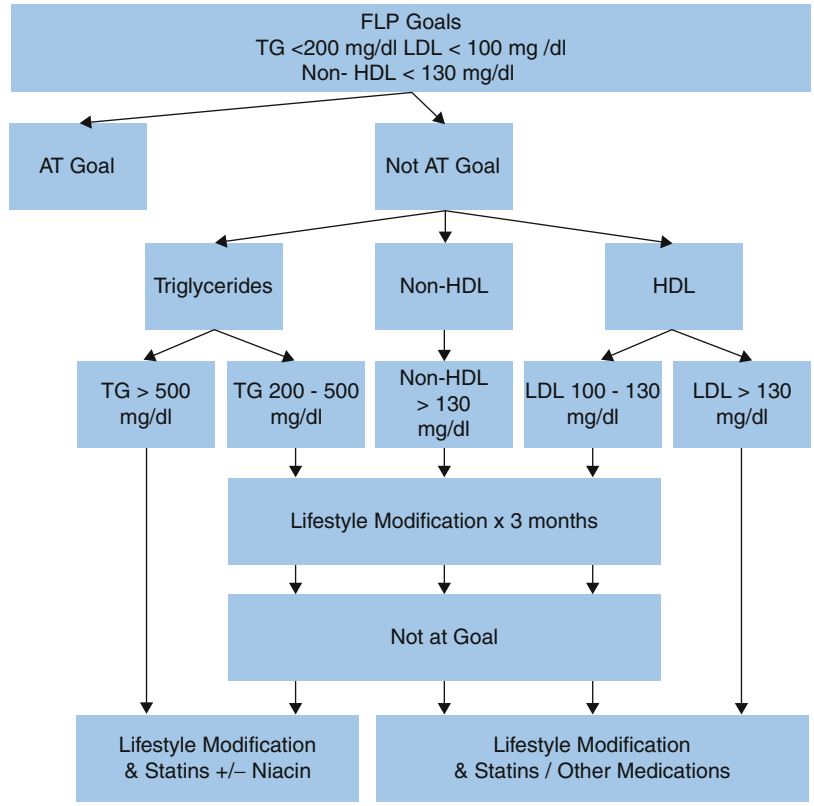

Fig. 3 Fasting lipid profile goals and posttransplantation hyperlipidemia treatment algorithm (Adapted from Pham et al. and Kasiske et al.)

(simvastatin, atorvastatin, lovastatin), CYP 450-2C9 pathway (fluvastatin), or sulfaction (pravastatin). Interactions with the CYP450-3A4 enzyme system may increase statin blood levels leading to myopathy and rhabdomyolysis. As such, the dose of atorvastatin and simvastatin is usually limited to 20 mg/day and pravastatin and fluvastatin to 40 mg/day, and hepatic enzyme levels are routinely checked.

Bone and Mineral Disease

At the time of transplantation, there may be significant abnormalities of bone remodeling related to chronic kidney disease. In SPK recipients, additional factors may exacerbate bone loss. Preexisting type 1 diabetes mellitus has been associated with low turnover bone disease and osteopenia. Further bone loss is associated with secondary hyperparathyroidism, often seen in progressive renal failure.

Abnormalities in phosphorous and calcium metabolism are seen early in the posttransplant course. Once the renal function improves and then stabilizes, many of the derangements in mineral metabolism are corrected. Many patients with chronic kidney disease who initially had hyperphosphatemia prior to renal transplantation may develop hypophosphatemia in the immediate perioperative period. The opposite effect may be seen with calcium, which increases early in the perioperative period. The etiology of both observations is secondary to elevated parathyroid hormone levels in the setting of a functioning renal graft. The hypophosphatemia and hypercalcemia tend to correct themselves analogous to improvements in the renal function, as that there is significant decrease of parathyroid hormone levels during the first 3 months after transplantation. Subsequent stabilization of the PTH occurs within the first year posttransplant (Sprague et al. 2008).

Despite correction of calcium and phosphorous, there is rapid decline in bone mineral density

in the early posttransplant period. Though the rate of bone loss may decelerate or cease by around 3 years posttransplant, bone mineral density remains below normal. Reduced calcium absorption, abnormal vitamin D, and choice of immunosuppression agents (particularly glucocorticoids) are among the factors contributing to the further weakening of bones and the risk of bone disease posttransplantation. This decrease in BMD among kidney transplant recipients results in a risk of bone fractures that is four times that of the general population.

Despite these data there is a paucity of randomized controlled trials addressing the optimal surveillance and management of bone and mineral disease after transplantation. The Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD guidelines for posttransplantation bone disease suggest measurement of calcium, phosphorous starting in the immediate posttransplant period with PTH, and alkaline phosphatase afterwards. BMD measurement is suggested in the first 3 months after transplantation when patients have an estimated GFR of 30 mL/min per 1.73 m^2. Treatment strategies are similar to those in CKD patients; utilizing vitamin D and calcitriol/alfacalcidol. In patients who are at higher fracture risk the use of bisphosphonates may be considered using bisphosphonates (KDIGO CKD-MBD Work Group 2009).

Infections

By virtue of being immunosuppressed, transplant patients have a higher likelihood of acquiring an infection and the severity of any infection will be higher as compared to a nonimmunocompromised individual. As specific aspects of infectious disease in transplantation are addressed elsewhere in this text, discussion will be limited only to urinary tract infections in the posttransplant population.

Urinary tract infections (UTI) are frequently diagnosed in pancreas transplant recipients and are a common reason for hospitalization. The frequency of UTIs is significantly higher in BD grafts (Pirsch et al. 1998). A possible reason for the high frequency of urinary tract infections in BD is possible urine reflux into the duodenal segment resulting in a blind pouch where bacterial overgrowth can occur. Other contributing factors include prolonged catheter drainage, bladder mucosal damage, and the presence of a diabetic neuropathic bladder with incomplete emptying. The need for complete bladder emptying in patients with neurogenic bladders often leads to the practice of self-catheterization, which also increases the incidence of UTIs. However, a patient with diabetes and a neuropathic bladder is not necessarily precluded from BD even in the presence of abnormal urodynamic studies.

The diagnosis of a symptomatic UTI requires a quantitative bacterial count ($\geq 10^5$) in an appropriately collected urine specimen in the presence of symptoms or signs of urinary infection. Pyuria is defined in the setting of quantified leukocytes per high power field as opposed to relying on a qualitative positive leukocyte esterase on a "dipstick." The most common causative organisms are Gram-positive cocci (Enterococcus) and Gram-negative rods (*E. coli*) (Vidal et al. 2012).

UTIs in transplant recipients should be considered complicated UTIs due to functional and structural abnormalities in these patients. The Gram stain performed on the urine specimen will help guide therapy. Until these data are obtained, an oral fluoroquinolone may be used empirically. If there is evidence of Gram-positive cocci on Gram stain, coverage for enterococcus with amoxicillin should be added until the causative organism is identified. A treatment course of 7–14 days is generally recommended.

Monitoring of Hematopoiesis

Anemia (defined as a hemoglobin <14 g/dL in males and <12 g/dL in females) is not uncommon posttransplantation, particularly in those patients who received a SPK. In most recipients, anemia generally peaks at two points: early in the posttransplant period after which hemoglobin levels normalize only to peak again years later (Vanrenterghem et al. 2003). Early in the perioperative period the etiology of anemia is multifactorial: surgical blood loss and inflammation,

initial use of high potency immunosuppression induction therapy leading to bone marrow suppression, and the cessation of erythropoietin-stimulating agents previously utilized in the pretransplant period. Eventually, in patients who are not iron deficient or have graft dysfunction, the anemia will resolve within 6–12 months after transplantation.

The causes of the second anemia peak (late in the transplant period) are once again multifactorial: decreased renal function, infections, and medications (immunosuppressive drugs, antiviral agents, and the use of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs)) (Afzali et al. 2006). The usual approach to patients with anemia consists in elucidation of its etiology, which in its most simplistic forms are: due to either decreased production, increased destruction, or blood loss. The initial workup consists of ordering a reticulocyte count, vitamin B levels (folate and B12), iron stores (serum iron, serum iron-binding capacity (transferrin), percent transferrin saturation), testing for hemolysis (indirect bilirubin, lactate dehydrogenase, haptoglobin), and screening for gastrointestinal blood loss. Depending on the results of this workup, management is either simple requiring correction of deficiencies or more complex requiring further input from a hematology consultant. In many cases, the use of an erythropoietin-stimulating agent may be required.

There are no ESA guidelines specific to the post-pancreas transplant population; however, extrapolations from landmark trials in chronic kidney disease and current FDA dose guidelines give some insight into the use of ESA in the transplant patient population (U.S. FDA 2011). It is reasonable to initiate these medications in the absence of iron deficiency once the hemoglobin has reached less than 10 g/dL and correct to a goal no greater than 11 g/dL. This is based on data showing that using ESAs to target a hemoglobin level of greater than 11 g/dL increased the risk of serious adverse cardiovascular events, such as heart attack and stroke, and provided no additional benefit to patients.

Interestingly, in up to 16% of SPK patients polycythemia (PTE) (as defined by a hematocrit $>$ 48% in women and $>$52% in men) has been described (Guerra et al. 2010). After ruling out malignancies, (commonly renal cell and hepatocellular carcinoma or breast cancer) PTE is often treated with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs). When these interventions are ineffective, therapeutic phlebotomies may be required.

Malignancy

With the advent of more profound immunosuppressive regimens, the incidence of organ rejection has decreased; however, an unintended consequence of this is an increase in the rates of malignancy in the immunosuppressed population as compared to those not immunosuppressed. Malignancies commonly seen in the nonimmunosuppressed population (lung, prostate, breast, colon, uterine, and cervix) are seen at similar rates in the immunosuppressed population. However, a variety of cancers have higher incidences in the immunosuppressed population as compared to the nonimmunosuppressed (lymphomas, squamous cell carcinomas of the lip and skin, Kaposi's sarcoma, carcinomas of the vulva and perineum, carcinomas of the kidney, and hepatobiliary tumors) (Penn 1990).

A well-described malignancy occurring posttransplantation is posttransplant lymphoproliferative disorder (PTLD). The cumulative incidence of PTLD after pancreas transplant varies from 1% to 7%. Despite its low incidence, the diagnosis of PTLD can significantly decrease graft survival. This condition is thought to be the result of hyperproliferation of lymphoid cells that arise in the setting of posttransplant immunosuppression (Penn 1990). The major risks for PTLD are recipient Epstein-Barr virus (EBV) seronegativity and an increased number of doses of lymphocyte depleting antibody therapy. Treatment depends on the extent, histology, and EBV positivity. Described strategies may include reduction or elimination of immunosuppression, anti-CD20 monoclonal antibody therapy (Rituximab), conventional chemotherapy, surgical excision, and radiotherapy (Issa et al. 2009).

Pregnancy Posttransplant

The first reported case of a successful pregnancy after SPK was reported in 1986. Despite data collected by the National Transplantation Pregnancy Registry (NTPR) and published case reports and series in patient who received a SPK transplant, there are few guidelines on the management of pregnancy in the pancreas transplant patient (Coscia et al. 2009). These data suggest that pregnancy after SPK transplantation has a similar risk profile of obstetric and perinatal complications as compared to pregnancy after kidney transplantation; hence, many of the guidelines from the experience in kidney transplant recipients are extrapolated to the SPK population.

Hypothalamic gonadal dysfunction in females with ESRD may explain why women of childbearing age (18–49 years) with ESRD have fertility rates nearly 10 times lower than their healthy counterparts. This hormonal dysfunction may be reversed within the first few months after kidney transplantation. In counseling patients wishing to become pregnant, opinion on the optimal timing after transplantation is equivocal. For kidney alone recipients, consensus opinion recommends that as long as graft function is optimal, defined as a serum creatinine <1.5 mg/dL, with <500 mg/24 h protein excretion, and no concurrent fetotoxic infections or use of teratogenic or fetotoxic medications, and immunosuppressive dosing is stable at maintenance levels, the patient can safely proceed with the pregnancy with estimates ranging from as little as 6 months to 2 years following transplant (McKay and Josephson 2008).

The management of pregnancies after transplantation must occur in the setting of a multidisciplinary team composed of transplant and high-risk obstetrics professionals. In normal pregnancy, there is marked increase in the GFR, as much as 50% above preconception measurements, leading to changes in immunosuppression drug serum levels. This requires close monitoring of drug levels given the narrow therapeutic index of these medications.

Pregnancies in transplant recipients are complicated by higher rates of hypertension, preeclampsia, prematurity, and lower birth weight as compared to the nontransplanted population. Perinatal mortality has been estimated at 5.8%. Interestingly, as babies born to transplant recipients are more likely to be born preterm, it is not surprising to expect that frequently these babies are considered to be of low birth weight (Wyld et al. 2013).

Immunosuppression Considerations

Although one large database reported the incidence of birth defects as similar to the proportion in the general population at 3–5%, the importance of minimizing the exposure to teratogenic drugs is of utmost importance. Studies show that the immunosuppressive agents most frequently utilized during pregnancy are azathioprine, calcineurin inhibitors (cyclosporin, tacrolimus), and steroids (prednisone). Reports associating the use of mycophenolate and structural defects in the developing fetus have placed special caveats on the use of this class of medications in women of child bearing age. Currently the US Food and Drug Administration (FDA) requires a risk evaluation and mitigation strategy (REMS) from manufacturers of mycophenolate (mycophenolate mofetil and mycophenolic acid) given the increased risk of first trimester pregnancy loss and congenital malformation associated with exposure to this class of medications during pregnancy. Given this risk, it is generally recommended that mycophenolate is avoided for at least 6 weeks prior to pregnancy. Additionally, European guidelines have similar caveats for sirolimus recommending its avoidance for at least 6 weeks prior to pregnancy (EBPG Expert Group on Renal Transplantation 2002).

Conclusions

The idiosyncrasies of the posttransplant surveillance and management of pancreas transplant recipients require specialized knowledge and experience. Clinicians need to be intimately aware of the particular issues that are unique to

this organ as knowledge in the management of other solid organs may not be directly transferable to pancreas transplantation. This chapter provides a brief overview of the major issues and topics. An extensive bibliography is provided for more detailed review.

Cross-References

- Infectious Issues After Pancreas Transplant
- Pathology of Pancreas Transplant
- Surgical Complications of Pancreas Transplant
- Surgical Technique of Pancreas Transplantation

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Infectious Issues After Pancreas Transplant

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Abstract

Despite improved clinical outcomes with pancreas transplantation, infectious complications remain a significant cause of morbidity and mortality in pancreas transplant recipients. The spectrum of organisms encountered ranges from routine community-acquired and nosocomial pathogens to rare opportunists. This broad spectrum, combined with the sometimes atypical presentation and rapid progression of illness, poses a challenge to the diagnosis and management of infections in transplant recipients. Although many of the fundamentals of diagnosis, management, and prevention of infections in solid organ transplantation apply to the pancreas transplant population, there are features that are unique to pancreas transplantation. While a comprehensive review of the wide spectrum of infectious diseases encountered in pancreas transplantation is outside the scope of this text, the most salient risk factors, epidemiology, timing, clinical features, treatment, and prevention of infection specific to pancreas transplantation is reviewed in this chapter.

Keywords

Pancreas transplant infection · Immunocompromised host · Immunosuppression complications

Introduction

Over the past few decades, advances in surgical techniques, immunosuppressive regimens, antimicrobial therapies, and monitoring of graft function have improved outcomes of pancreas transplantation surgery. However, infection continues to be one of the most common and major causes of morbidity and mortality in pancreas transplant recipients. Infectious complications significantly impact length of hospital stay and readmissions, patient and graft survival, and healthcare expenditure (Singh et al. 2008). Published data from some pancreatic transplantation centers have demonstrated that 75–80% of recipients experience at least one infectious complication (Herrero-Martinez et al. 2013; Bassetti et al. 2004), with some studies even reporting an incidence as high as 94% (Fontana et al. 2009).

Infectious complications can range from the more mundane community-acquired or healthcare-associated bacterial and viral pathogens to opportunistic diseases uncommonly seen in immunocompetent hosts. The broad differential for infection, compounded by the rapid progression and atypical presentation of disease processes due to attenuated inflammatory responses, altered anatomy, antimicrobial resistances, and potential for drug toxicities and interactions can create challenges in the timely, accurate, and aggressive diagnosis and treatment of infection in transplant recipients. While many of the principles of diagnosis, management, and prevention of infection remain similar among all types of organ transplantation, there are features unique to pancreas transplantation. This chapter will provide an overview of general transplant-related infectious complications, with additional focus on those that are specific to pancreas transplants. Collaboration with infectious diseases consultants is essential in optimizing the approach to diagnosis and treatment of these infections.

Risk Factors

Underlying host factors, epidemiologic exposures, operative techniques, posttransplant immunosuppressive regimens, and rejection create a dynamic interplay that determines the ever-changing risk of infection in pancreas

transplantation. The "net state of immunosuppression" refers to the composite effect of all the factors that contribute to the patient's susceptibility to infection (Fishman and Rubin 1998) and provides a useful framework to define, diagnose, and manage infections in transplant recipients. The risk of infection changes at different stages in the posttransplantation period, and currently, there are no assays or tests available to accurately calculate the risk of infection at any given time period. The risk of infection depends on a multitude of donor/recipient, surgical, and immunological risk factors that can be classified as pretransplant, operative, and posttransplant.

Pretransplant

Age

Data from US centers suggest an increased risk of mortality in pancreas transplant recipients older than age 45 (Gruessner and Sutherland 2005; Wiseman 2009). Recipient age at the time of transplantation impacts both the risk and severity of infection, especially in the first-year posttransplant (Rostambeigi et al. 2010). While the rate of organ rejection is lower in older recipients, there is a lower incidence of graft survival and higher graft and postoperative complications, which indirectly increase their infection risk. A higher incidence of pulmonary infections in older patients has also been documented (Ablorsu et al. 2008). Immune senescence and poor nutritional status associated with advanced age are proposed mechanisms for the higher risk of infection observed in older transplant recipients (Gelson et al. 2010). However, there is limited evidence confirming this risk, and more recent studies have shown similar patient and graft survival outcomes in patients over the age of 50 (Schenker et al. 2011; Afaneh et al. 2011). While the mean age of pancreas transplant recipients continues to increase, data on older recipients remain limited, and overall, patients receiving pancreas transplants have a lower mortality than those on waiting lists regardless of age (Ojo et al. 2001).

Diabetes Mellitus

As the major underlying cause for pancreatic transplantation, the severity and duration of diabetes and its associated complications increase the risk of infection posttransplant. The association between diabetes and surgical site infections has been well characterized, and data extrapolated from renal transplantation indicate both increased risk of infection and allograft rejection in diabetic patients (Thomas et al. 2001). In addition, osteoarticular infections remain a hallmark of infections in pancreas transplant recipients, especially in the first-year posttransplant (Lumbreras et al. 1995). Vascular injury and the presence of sensory neuropathy contribute to ulcer formation and subsequent infection. Impaired local inflammatory responses, wound healing, and delivery of antibiotics to the affected area also adversely affect resolution of infection. Hyperglycemia-mediated effects on macrophage and neutrophil chemotaxis, adherence, and function also may explain the increased risk of infection (Delamaire et al. 1997). Autonomic neuropathy and neurogenic bladder secondary to diabetes also increase the risk of urinary tract infections, which can predispose to graft pancreatitis in bladder-drained pancreatic transplants as well as affecting renal allograft function in simultaneous pancreas kidney transplant (SPK) recipients. Preexisting renal transplantation for diabetic nephropathy and effects of prior immunosuppressive therapy also impact the risk of infection in pancreas after kidney (PAK) transplant recipients. The association of pretransplant peritoneal dialysis and risk of surgical site infections in SPK or PAK is controversial (Padillo-Ruiz et al. 2010; Kim et al. 2005).

Other

As with any other solid organ transplant, other pretransplant factors that must be considered when assessing risk of infection include both recipient- and donor-derived infections and epidemiologic exposures. As with all surgical procedures, patients with high body mass index are at increased risk for postoperative wound infection.

Skin and mucosal colonization with organisms like MRSA and *Candida albicans* is more common in diabetics and may predispose to postoperative skin, wound, and bloodstream infections with these organisms (Graham et al. 2006; de Leon et al. 2002). Similarly, prior exposures (prior infections with resistant organisms, total parenteral nutrition and catheter use, mechanical ventilation, etc.) leading to pretransplant colonization or continued infection in either the recipient or donor can affect both the risk and type of infections after transplant. Active infection in the recipient should be eradicated prior to transplantation, if possible. Donor-derived risk factors include chronic or latent infections that are screened for prior to transplant, such as Epstein-Barr virus (EBV), cytomegalovirus (CMV), toxoplasma, hepatitis B, or hepatitis C as well as unexpected latent infection such as tuberculosis or histoplasmosis and unrecognized bacteremia/fungemia/viremia in the donor at the time of organ procurement (Green 2013). Finally, pancreas transplantation in HIV-infected recipients is still relatively rare. So far only a handful of cases in well-controlled HIV patients have been reported, and data on the impact of preexisting HIV on risk of infection in pancreas transplantation is limited. A case review of four HIV-infected SPK recipients included one death due to Pseudomonas infection but no report of AIDS defining illnesses (Miro et al. 2010).

Surgical

Differences in surgical techniques as well as intraoperative factors influence both the risk and type of postoperative infections. The route of drainage of pancreatic exocrine secretions (bladder vs. enteric) impacts the incidence and microbiology of urologic and intra-abdominal infections.

Bladder drainage was introduced in 1983 as an alternative to enteric drainage to reduce the risk of intra-abdominal abscess due to enteric leaks (Cook et al. 1983). Drainage of pancreatic exocrine secretions into the bladder seems to be associated with decreased intra-abdominal infections, but even with bladder drainage, the incidence of intra-abdominal infections remains fairly high (Sollinger et al. 1991). In addition, bladder drainage has been associated with a higher incidence of infections secondary to increased rate of urologic complications and urinary tract infections (60% compared to 9.6% in enteric drainage) (Michalak et al. 2005). Pancreatic exocrine secretions alkalinize the bladder and account for much of the higher rate of symptomatic UTIs in recipients as well as increasing sterile cystitis, balanitis, urethritis, and urethral stricture. In some cases, a foreign body such as an exposed suture can act as a nidus for UTIs or stone formation. Urinary tract and peritoneal infections can also occur from either contiguous spread of bacteria from the donor duodenum or anastomotic leaks. Reflux pancreatitis secondary to reflux of urine in bladder drainage can result in acute inflammation of the pancreas graft, which can mimic acute rejection, and often the urine is colonized with bacteria, especially in patients with neurogenic bladder. In one series of 388 bladder-drained pancreas transplants, 23.8% of patient required conversion to enteric drainage due to recurrent urologic complications/infections. These authors also found a lower risk of opportunistic infections such as CMV with enteric drainage (Sollinger et al. 1998).

Over time, enteric drainage has thus become the favored technique for reconstruction secondary to more physiologic release of pancreatic enzymes and decreased incidence of urologic infections. Enteric drainage has been associated with higher incidence of candidal and intra-abdominal infections (Sollinger et al. 1991), but improved selection of suitable cadaveric grafts and perioperative prophylaxis has helped mitigate the risk of intra-abdominal infections. More efficacious immunosuppression has also reduced the incidence of acute rejection, which indirectly decreases risk of infection associated with more intensive antirejection therapy.

Among the different types of pancreatic transplantations (pancreas alone vs. PAK vs. SPK), studies have demonstrated a higher and more prolonged risk of infection in SPK recipients. In one study, the incidence of infection in PAK and pancreas transplant alone (PTA) peaked during the first month posttransplant with rapid decline in rate of infections over 3–6 months, while the

SPK group not only had the highest incidence of infections in the first month but sustained an increased risk over a 90-day time period (Bassetti et al. 2004). Infectious complications have also been documented to be the leading cause of morbidity and mortality among SPK recipients, with bacterial UTI and wound infections ranking as the most common sites of infection (Linhares et al. 2004; Michalak et al. 2005). Historically, higher rates of rejection after SPK requiring increased immunosuppression has been the proposed explanation for the increased risk of routine and opportunistic infections. Some authors have also proposed that SPK patients have the highest incidence of infections among the three types of PT due to worse nutritional status, more severe illness secondary to uremia, and longer waiting list times (Bassetti et al. 2004). Longer operative times in SPK compared to the other groups may also play a role in risk of infection. However, a more recent study failed to show difference in incidence of infection among PAK versus PTA versus SPK groups (Rostambeigi et al. 2010).

As with all types of organ transplantation, other factors contributing to the development of postoperative infection include the need for surgical re-intervention and pulse dose steroids for rejection (Green 2013). Preexisting peripheral arterial disease, longer cold ischemia times, and higher transfusion requirements increase the risk of ischemic injury to the allograft and associated risk of infection (Herrero-Martinez et al. 2013). Contamination of the graft or operative field, bleeding at surgical sites, and prolonged operative times have all been associated with variable infection risk. Despite use of routine nasogastric decontamination of the donor upper GI tract, contamination of the preservation solution for pancreas allografts is higher than in other organ transplants secondary to bacterial colonization of the duodenal segment (Berger et al. 2006).

Posttransplant

Infections posttransplant can be categorized as due to reactivation of latent infections in the recipient, acquired from the donor organ, or new healthcare-associated and community-acquired pathogens.

Immunosuppression is the major determinant of infection risk posttransplant. Although the degree and nature of risk vary with different immune-modulators, any of these agents will have at least some impact on the risk of routine as well as opportunistic infections. Allograft rejection and the concomitant intensification of immunosuppression not only further increases the risk of infection but also resets the expected time interval for reactivation of latent infections posttransplant. Rejection itself may also present similarly to infection and must be considered in the differential for posttransplant fever.

Sequelae of operative complications such as postoperative hematomas, fluid collections, devitalized injured tissue, and the need for indwelling foreign catheters can predispose to posttransplant infection. Technical complications that affect the vascular supply and function of the allograft can create a nidus for infection, and consequences of uncorrected technical issues such as hematomas, seromas, and necrosis can lead to recurrent or relapsing infections.

Prolonged postoperative use of central venous catheters, Foley catheters, and endotracheal intubation can predispose to bloodstream infections, urinary tract infections, and pneumonia, respectively, as well as increase the risk of colonization and subsequent infection with multidrug-resistant (MDR) organisms. Therefore, ongoing assessment of the necessity of these catheters should be undertaken with the goal of removal as soon as possible. Nosocomial exposures to *Legionella*, *Aspergillus*, and multidrug-resistant pathogens can lead to potentially life-threatening infections in the immunocompromised transplant recipient. Although the risk has been mitigated with improved screening, all transplant recipients are also at risk for developing infection with transfusion-associated pathogens (Mezochow et al. 2015). Patients undergoing transplant during winter months may also be exposed nosocomially to seasonal virus outbreaks such as RSV, influenza, and rotavirus.

Finally, community exposures are an important potential source of posttransplant infection after organ recipients are discharged from the hospital.

These exposures may vary from common community-acquired viral infections to less commonly seen pathogens that may be related to occupational or travel-associated risk factors. Pathogens and infections such as respiratory viruses, *Aspergillus*, *Nocardia*, *or Cryptococcus neoformans* that may normally be benign or self-limited in normal hosts can lead to major infectious complications posttransplant. Thus, recipients must be counseled about practices to prevent exposures and infection, and compliance with antimicrobial prophylaxis must be emphasized.

Timing of Infections

The timing of infections post-pancreatic transplantation follows the same general pattern as seen with other solid organ transplants. The risk of infection is usually the highest in the first 90–180 days posttransplantation, coinciding usually with the most intense immunosuppression and postoperative periods. Deaths due to infection peak during this time period as well as in 3–12 months posttransplant (Gruessner et al. 2010). However, the use of antimicrobial prophylaxis and newer immunosuppressive agents has altered the expected timeline for infection (Fishman 2007). For example, corticosteroids and azathioprine for induction immunosuppressive therapy have largely been replaced by calcineurin inhibitors, sirolimus, and T/B cell-depleting agents. The effects of lymphocyte-depleting induction therapies can last for months after administration and amplify viral replication, even later in the posttransplant course than typically expected. Similarly, the routine use of *Pneumocystis jiroveci* (PJP) prophylaxis has decreased the incidence of PJP pneumonia, and the use of cytomegalovirus and fungal prophylaxis has shifted the time frame for these infections later into the posttransplant period. Any intensification of immunosuppression for rejection or surgical re-intervention can reset the timeline for infection. Nevertheless, stratification of infection risk based on time interval from transplantation provides a useful framework to assess the risk of infection, create a differential diagnosis for infection posttransplant, and design strategies for antimicrobial prophylaxis (see Table 1). The time intervals for infection are usually classified as early (0–30 days posttransplant), intermediate (30–180 days posttransplant), and late (greater than 180 days posttransplant).

Early (First 30 Days)

The incidence of infections is highest during the first month posttransplantation with all types of pancreas transplantation (PTA, PAK, and SPK), but the risk continues to remain higher for up to 90 days following SPK transplantation (Bassetti et al. 2004). Early infections are usually related to preexisting conditions and complications of surgery and hospitalization. Catheter-associated bacteremias, nosocomial pneumonias, surgical site infections, and *Clostridium difficile* (C. diff) diarrhea constitute the most common causes of infection in the immediate posttransplant period (Bassetti et al. 2004; Fishman 2007). Technical complications such as anastomotic leaks/stenosis or graft injury can lead to sequelae such as abscesses and other invasive infections. Bacteria and fungi (especially yeast) are the causes of infection in the early posttransplant period, and approximately 50% of bacterial infections posttransplantation occur in the first month (Al-Hasan et al. 2009; Green 2013) Donor-derived bacterial and fungal infections as well as viremia may also present during this time period. Herpes-simplex virus (HSV) reactivation can also occur in the first month, but is less common now with the use of antiviral prophylaxis. In general, other opportunistic infections are rare as the full consequences of immunosuppressive therapy have not yet taken effect.

Intermediate (30–180 Days)

The incidence of bacterial and fungal infections continues to remain high in the early intermediate period. Wound and intra-abdominal infections predominate in the first 3 months posttransplant, and approximately two-thirds of all invasive fungal

Table 1 Timeline of common infections posttransplantation

	Early (<1 month)	Intermediate (1–6 months)	Late (>6 months)
Donor-derived	Bacteremia West Nile virus LCMV HIV **Without prophylaxis:*** Primary HSV Candidiasis	Hepatitis C Tuberculosis **Without prophylaxis:** Primary EBV Primary CMV Hepatitis B	Hepatitis C Hepatitis B Endemic mycoses HTLV JC (PML) Tuberculosis
Nosocomial	SSIs Bacteremia Candidemia Urinary tract infections Pneumonia Clostridium difficile	SSIs *Clostridium difficile*	*Clostridium difficile*
Viral (reactivation or acquired)	**Without prophylaxis:** HSV Respiratory viruses	**Without prophylaxis:** CMV EBV/PTLD VZV HSV Hepatitis B **With prophylaxis:** BK virus (PAK, SPK only) Hepatitis C Adenovirus Respiratory viruses	Late onset CMV Hepatitis B Hepatitis C HSV JC (PML) EBV/PTLD HPV VZV Respiratory viruses
Atypical bacterial		Tuberculosis Atypical *Mycobacteria* **Without TMP-SMX:** *Nocardia* *Listeria*	*Nocardia* *Rhodococcus* Tuberculosis Atypical *Mycobacteria*
Fungal	Candidiasis *Aspergillus* (recipient colonization)	**With azole prophylaxis:** *Aspergillus* Candidiasis (azole resistant) **Without prophylaxis:** Pneumocystis jiroveci Candidiasis *Cryptococcus*	*Cryptococcus* Endemic Mycoses *Aspergillus* Zygomycetes
Parasitic		*Strongyloides* *Trypanosoma cruzi* **Without prophylaxis:** Toxoplasmosis	*Strongyloides* *Trypanosoma cruzi* Toxoplasmosis

*Prophylaxis refers to antiviral (CMV, HBV), antifungal (fluconazole), and PJP (TMP/SMX). The risk of infection varies at different stages of the posttransplant period, but the timeline of infections may be altered depending on intensity of immunosuppression, allograft rejection, duration of prophylaxis, etc. Abbreviations: *HSV* herpes simplex virus, *CMV* cytomegalovirus, *VZV* varicella-zoster virus, *EBV* Epstein-Barr virus, *PTLD* posttransplant lymphoproliferative disorder, *HPV* human papillomavirus, *SSI* surgical site infections, *HTLV* human T lymphocytic virus, *PML* progressive multifocal leukoencephalopathy, *LCMV* lymphocytic choriomeningitis virus

infections occurred within the first 2 months in one series (Lumbreras et al. 1995). As antibiotic use is the major trigger for symptomatic C. diff disease, there is no specific time frame for this complication.

The intermediate period has been classically associated with the emergence of opportunistic infections. In the absence of prophylaxis, CMV is the most frequent pathogen in the second and

third months posttransplant (Lumbreras et al. 1995). Prophylaxis with trimethoprim-sulfamethoxazole (TMP/SMX) provides protection against PJP, toxoplasmosis, *Listeria*, UTIs, and susceptible *Nocardia* species, but otherwise, these pathogens can also manifest in the intermediate period along with EBV-associated posttransplant lymphoproliferative disorder (Paya et al. 1999). In the presence of standard antimicrobial prophylaxis, uncovered viral pathogens and allograft rejection are responsible for the majority of febrile episodes (Fishman 2007). Herpesvirus infections are also uncommon with antiviral prophylaxis. Antifungal prophylaxis with fluconazole is routinely used and should protect against endemic fungi. In general, with antimicrobial prophylaxis, many of the classic opportunistic infections now occur later once prophylaxis is discontinued.

UTIs resistant to TMP/SMX as well as *Aspergillus*, *Strongyloides*, and *Trypanosoma cruzi* infections can also manifest during the intermediate period (Green 2013).

Late (>180 Days)

Typically, the incidence of infection is expected to decrease after the first 6 months of infection as immunosuppression is generally lowered in patients with adequate allograft function and routine community-associated infections predominate. Overall, infections within the first year and afterward are still predominantly bacterial (Rostambeigi et al. 2010) with some studies reporting a second peak in fungal infections after 12 months (Lumbreras et al. 1995). However, the risk of opportunistic infections is never fully mitigated, and the risk of infection varies with intensification of immunosuppression, need for surgical re-intervention, and epidemiologic exposures. Graft-related dysfunction and uncorrected anatomical or functional abnormalities continue to pose a risk for late infections, as do procedures required to correct these problems. Duration of prior antimicrobial prophylaxis may influence the risk of later infections; for example, Pneumocystis pneumonia or CMV may occur later in patients who have received prolonged or intermittent prophylaxis (Humar and Snydman 2009). Viral processes such as PTLD, BK virus, varicella-zoster virus (VZV) and HSV, as well as viral-associated anogenital carcinoma can also occur (Green 2013).

Types of Infections

Bacterial

Bacterial infections not only account for the majority of infectious complications in the immediate postoperative period and the first-year posttransplant but also 78% of infections beyond the first year, regardless of the type of pancreas transplantation (PTA vs. PAK vs. SPK) (Rostambeigi et al. 2010). Depending on the type of drainage (bladder vs. enteric), urinary tract infections (UTIs) or surgical site infections are most common, followed by bacteremia, pneumonia, intra-abdominal infections, cellulitis/osteomyelitis, and C. diff (Herrero-Martinez et al. 2013). As described above, the risk of nosocomial bacterial infections is related to underlying host, operative, and postoperative factors/complications.

The urinary tract is the leading site of infection in bladder-drained pancreas transplant recipients with a frequency as high as 80% in some studies (Smets et al. 1997). The most common urinary pathogens include gram-negative aerobes and *Enterococci* along with *Candida* species (Fontana et al. 2009). Risk factors associated with development of UTIs include prolonged urinary catheterization, hemodialysis, and perioperative antibiotic prophylaxis in excess of 48 h (Lapchik et al. 1992) as well as the use of ureteral stents (Nicol et al. 1993). Use of TMP-SMX for PJP prophylaxis also decreases the incidence of UTIs caused by organisms susceptible to this antibiotic (Tolkoff-Rubin et al. 1982), so that the infections that occur will likely be resistant. Diagnosis of UTI is based on clinical suspicion as well as urinalysis and urine culture, as transplant recipients may not manifest the usual symptoms of dysuria or frequency but instead just present with fever or unexplained leukocytosis.

Surgical site infections (SSIs) including superficial wound infections and intra-abdominal infections are a major cause of morbidity and potentially graft loss and mortality in pancreas transplant recipients (Smith et al. 1992). SSIs can be classified as superficial (above the fascia), deep (below the fascia), and combined (superficial and deep compartments involved). Reported rates of superficial and deep wound infections have varied from 7% to 50% among different centers (Bassetti et al. 2004) with approximately 10–40% superficial, 15–22% deep, and 8% combined (Everett et al. 1994; Hesse et al. 1986). SSIs commonly occur within the first 30 days of transplantation but may present later; in one series, 58% of SSIs occurred beyond 30 days (Bassetti et al. 2004). Infections are typically polymicrobial, with common pathogens including gram-positive organisms (*Staphylococcus aureus*, coagulase-negative *Staphylococci*, and *Enterococci*), enteric gram-negative rods (*Morganella*, *Proteus*, *E. coli*, etc.), and anaerobes (*Bacteroides* and *Peptostreptococcus*) (Lumbreras et al. 1995; Michalak et al. 2005; Smets et al. 1997) as well as fungal pathogens (*Candida* species). Expected pathogens depend on the type of procedure and drainage. In SPK and bladder-drained pancreas transplantation, etiologic agents include the gram-positive and gram-negative aerobes endogenous to the skin and bladder, whereas with enteric drainage, anaerobes must also be considered. Diagnosis may not be obvious, as findings may be nonspecific (fever and leukocytosis), and even wound drainage may have a relatively innocuous appearance. Delays in timely diagnosis and therapy can lead to impaired wound healing and other significant morbidity as well as mortality. Any wound drainage should be sent for gram stain and culture, and imaging should be utilized to look for any deeper infections with opening of the incision, percutaneous drainage, or surgical exploration and debridement as appropriate. Initial empiric broad-spectrum antimicrobial therapy should be utilized with narrowing based on culture results. Consideration should also be given to immunosuppression, especially in life-threatening cases. If there is suspicion for graft involvement, early surgical exploration, repair of any anastomotic leaks, and even graft pancreatectomy may be appropriate to minimize morbidity and mortality. Development of mycotic aneurysm at the arterial anastomosis is an indication for urgent transplant pancreatectomy, prior to arterial rupture.

Bloodstream infections occur frequently in pancreas transplant recipients with common sources including vascular access (catheters or fistulae) as well as secondary seeding from SSIs, UTIs, pneumonia, anastomotic leaks, gastrointestinal translocation, and diabetic foot infections. Bacteremia has been associated with mortality, graft loss, and acute rejection episodes (Singh et al. 2008). Due to immunosuppression, fever may not always be present, and other clues may be limited to isolated leukopenia or leukocytosis or hypotension in the appropriate clinical context. Blood cultures should be obtained from multiple separate venipunctures, and confirmation of bacteremia should prompt removal of intravascular lines and other catheters as well as work-up of other secondary sources. Most cases of bacteremia occur in the first-year posttransplantation, with preponderance of gram-positive organisms in early bacteremia (first month) (Berger et al. 2006) unless the source is the urinary tract (Smets et al. 1997). While the prevalence of resistant organisms will vary with each transplant center, high rates of resistant pathogens (MRSA, VRE, multidrug-resistant gram negatives) have been reported, and broad-spectrum empiric therapy should be initiated while awaiting culture results.

Postoperative pneumonia occurs in 5–15% of pancreas transplant recipients (Fontana et al. 2009). Common pathogens include *Staphylococci* and gram-negative aerobes, but *Legionella* should be also considered in the appropriate clinical setting. Active CMV pneumonitis is a risk factor for development of concomitant bacterial pneumonia. Other risk factors for postoperative pneumonia include prolonged mechanical ventilation and intubation, pulmonary edema, and intense immunosuppression or antirejection therapy. Aggressive drainage and culture of associated pleural effusions in cases of suspected pneumonia should be pursued as the progression to empyema in

transplant recipients is associated with high mortality.

Viral

Cytomegalovirus (CMV)

CMV is a herpesvirus with seroprevalence rates of 30–97% in the general population and is the most common viral infection in pancreas transplant recipients (Axelrod et al. 2005). In the absence of prophylaxis, CMV infection occurs in up to 71% of pancreas transplant recipients, usually in the first 3 months posttransplant (Lumbreras et al. 1995; Razonable and Humar 2013). Routine use of preventive therapy has extended the timeline for development of CMV disease to the first year after completion of prophylaxis (Parsaik et al. 2011). CMV can directly cause invasive disease as well as exerting secondary immunomodulatory effects that impact allograft function/rejection (Rubin 1989) and increasing the risk of other infectious complications such as EBV-related PTLD (Walker et al. 1995), bacteremia (Munoz-Price et al. 2004), or invasive fungal disease (George et al. 1997). Clinical manifestations can range from asymptomatic viremia to end-organ failure. The development of symptomatic disease is directly related to the absolute viral load, the degree of change in viral load, and the intensity of immunosuppression (Emery et al. 2000). Therefore, primary infections occurring in seronegative (no preexisting immunity) recipients from seropositive donors (D+/R-) generally are the highest-risk category for severe disease. In cases where both the donor and recipient are seropositive (D+/R+), superinfection can occur and is usually of intermediate severity. Reactivation disease in D-/R+ cases is usually milder (Dunn and Najarian 1991). The use of lymphocyte-depleting agents such as antithymocyte globulin (ATG) or antilymphocyte antibodies is associated with CMV disease (Portela et al. 1995), whereas a lower risk has been seen with the use of mTOR inhibitors such as sirolimus (Brennan et al. 2011).

The most common manifestation of CMV disease, "CMV syndrome," is a mononucleosis-like syndrome characterized by fever, malaise, myalgias, and leucopenia with few or no focal symptoms. Symptoms and signs of tissue-invasive CMV disease depend on the affected end-organ with presentations including pneumonitis and ulcerative disease in any or all portions of the GI tract with possible severe complications of bleeding or perforation, pancreatitis, hepatitis, chorioretinitis (late manifestation), or meningoencephalitis (uncommon). Diagnosis previously relied on histopathology, culture, or serologic methods, but the development of antigen assays and more recently the use of nucleic acid testing (PCR) have significantly transformed the approach to both diagnosis and management of CMV disease. However, as serum PCR and antigen assays may be negative in cases of CMV retinitis, meningoencephalitis, or gastrointestinal disease, invasive procedures such as lumbar puncture for CSF specimens for PCR testing/culture or endoscopy with biopsy for histology are required. CMV culture is still utilized for resistance testing in patients who fail to respond to first-line treatments.

Prophylactic approaches (discussed in more detail below) include both universal prophylaxis (all at risk patients) and preemptive treatment (initiation of therapy in asymptomatic patients with early CMV replication based on PCR or antigen testing). First-line treatment of CMV disease includes IV ganciclovir (5 mg/kg q12 h with modification based on creatinine clearance), the preferred approach for severe symptomatic disease, or oral valganciclovir (900 mg twice daily with modification based on creatinine clearance), an acceptable alternative for non-severely ill patients with intact gastrointestinal absorption (Asberg et al. 2007). Treatment should continue for at least 2 weeks, dependent on resolution of clinical symptoms and of viremia. This latter is monitored weekly using PCR or antigen assays. Following completion of full dose therapy, secondary prophylaxis (lower dose oral valganciclovir) versus close clinical/lab monitoring should be considered for 1–3 months, depending on the clinical situation (Razonable and Humar 2013). In cases where CMV viremia does not improve on ganciclovir, testing of the viral isolate for resistance mutations is appropriate. Specific mutations may

confer resistance to ganciclovir alone (UL97 gene) or to multiple antiviral agents (UL54 gene). Foscarnet and cidofovir are active against CMV, but adverse side-effect profiles including significant nephrotoxicity limit their use to cases of ganciclovir-resistant CMV disease, depending on the specific resistance mutation found.

Epstein-Barr Virus (EBV) and Posttransplant Lymphoproliferative Disorder (PTLD)

EBV infection in transplant recipients may manifest as a mononucleosis syndrome, hepatitis, or pneumonia. However, PTLD remains one of the most severe posttransplant EBV-associated complications. The spectrum of PTLD ranges from asymptomatic lymphoid hyperplasia to malignant localized or disseminated lymphomas. The incidence of PTLD in the adult SOT population is approximately 3–10%, with reported mortality rates of 40–60% (Preiksaitis and Keay 2001; Paya et al. 1999). Studies specific to pancreas transplantation are limited, but in two single center studies, similar rates were found (Issa et al. 2009; Paraskevas et al. 2005). PTLD occurs most commonly in the first-year posttransplant (classically in the first 2–3 months), but a second peak of disease has also been noted at 7–10 years posttransplantation (Caillard et al. 2012). The majority (>90%) of early disease is B cell in origin, while later disease may be EBV-negative and is usually T, NK, or null cell in origin. Seronegative recipients with primary EBV infection posttransplantation have a 10–76-fold higher risk for development of PTLD than recipients who were already seropositive pretransplant (Preiksaitis 2004). Other risk factors for PTLD include use of antilymphocyte antibodies and OKT3, CMV mismatch or CMV disease, allograft rejection, and older recipient age (Allen and Preiksaitis 2013). Clinical presentations can include unexplained fever, mononucleosis-like syndrome (fever, pharyngitis, tonsillitis, lymphadenopathy), GI bleeding or obstruction, infiltrative disease of the allograft, abdominal mass lesions, hepatocellular or pancreatic dysfunction, or central nervous system disease. Diagnosis involves quantitative PCR, flow cytometry, nucleic acid testing of tissue, and histopathology. Management involves reduction of immunosuppression, anti-CD20 monoclonal antibody (rituximab), cytotoxic chemotherapy, surgical resection/irradiation, or rarely infusion of EBV-specific cytotoxic T lymphocytes. There is no definitive evidence to support use of antiviral monotherapy for treatment, and data on the utility of antivirals as a preventive strategy are limited.

Other Herpes Viruses

Prior to the routine use of CMV prophylaxis, HSV reactivation occurred in 35–68% of SOT recipients, usually in the first 2 weeks posttransplantation (Wilck et al. 2013). Roughly half of these recipients have symptomatic disease (oral or genital lesions). Compared to immunocompetent hosts, SOT recipients may have more severe disease with prolonged viral shedding (Greenberg et al. 1987). Other manifestations of HSV can include disseminated mucocutaneous disease including esophagitis, keratitis, hepatitis, encephalitis, and pneumonitis. Primary HSV infection posttransplantation can rarely be acquired from the donor organ and can present as a severe sepsis-like syndrome with hypotension and disseminated intravascular coagulation (DIC). VZV reactivation posttransplant (zoster) usually occurs later than HSV, with an incidence of approximately 10% in the first 4 years posttransplant (Pergam et al. 2013). Primary infection (chicken pox) is rare but can cause severe skin disease, pneumonitis, DIC, and encephalitis. Oral therapy with acyclovir, valacyclovir, or famciclovir is adequate treatment for mucocutaneous HSV or dermatomal zoster. IV acyclovir is utilized in cases of primary VZV infection, severe visceral or disseminated HSV or VZV, and ophthalmic involvement of zoster. VZV immune globulin is indicated for up to 10 days in a seronegative recipient with exposure to someone with active disease and should be given as soon as possible. Like the other herpesviruses, human herpesvirus-6 (HHV-6) disease is usually reactivation and rarely from primary infection. Active HHV-6 infection in SOT recipients is usually asymptomatic but can cause fever, rash, hepatitis, gastroduodenitis, colitis, pneumonitis, and encephalitis. HHV-6

can also exert immunomodulatory effects that may predispose to viral and fungal coinfections or allograft rejection. CMV prophylaxis reduces the incidence of HHV-6 viremia posttransplant, but routine use of HHV-6 prophylaxis or preemptive therapy is not recommended. HHV-8, which causes Kaposi's sarcoma and, less commonly, Castleman's disease and primary effusion lymphoma, can also cause fever, bone marrow suppression, hemophagocytic syndrome, and clonal gammopathy posttransplant but is more geographically limited with highest incidence in central and southern Africa, Middle East, and Mediterranean countries. Although cases of donor organ transmission have been documented, like the other herpes viruses most cases are due to reactivation of latent disease in the recipient. Kaposi's sarcoma lesions have been reported to occur in approximately 15% of HHV-8-positive patients in the first 3 years posttransplant (Lebbe et al. 2013).

Other Viruses

BK virus complicates renal transplants (SPK or PAK), causing viruria, nephropathy, and renal allograft failure. Higher serum BK viral loads are more specifically associated with BK nephropathy, which correlates better with high serum, as opposed to urine BK viral loads. Other polyomaviruses like JC virus, the cause of progressive multifocal leukoencephalopathy, are rare after SOT.

Respiratory viruses such as respiratory syncytial virus (RSV), adenovirus, and influenza virus may produce significant morbidity and mortality, and their identification has potential therapeutic implications. Early therapy for influenza is recommended in suspected or confirmed cases. The use of ribavirin for RSV in immunocompromised populations has been reported but with variable clinical efficacy. Ribavirin and cidofovir have been used for adenovirus, also with uncertain efficacy.

Fungal

Pancreas transplantation, akin to liver and small bowel transplantation, carries a higher risk of severe fungal infections compared to other types of solid organ transplants. The incidence of fungal infections in pancreas transplantation has been reported to be as high as 40% (Paya 1993). Despite the universal use of low-dose fluconazole prophylaxis, the incidence in one series continued to remain high at 28% (Herrero-Martinez et al. 2013). Fungal infections have been linked with graft dysfunction and contribute to significant morbidity and mortality. Sources of fungal infection include catheters, oral and gastrointestinal colonization, environmental sources (*Aspergillus*/*Zygomycetes*, endemic fungi, *Cryptococcus*), and donor-derived infections. Underlying diabetes and immunosuppression from prior renal transplantation in cases of PAK transplants have been proposed to contribute to the increased risk of fungal infections after pancreas transplantation (Paya 1993). Pretransplant peripheral arterial disease, longer operative cold ischemia times, and higher transfusion requirements have been associated with the development of fungal infections (Herrero-Martinez et al. 2013). Widespread use of broad-spectrum antimicrobials and antibacterial prophylaxis have also been linked with higher rate of resistant fungal pathogens.

Candidiasis predominates as the leading type of fungal infection in pancreas transplantation (Smets et al. 1997; Rostambeigi et al. 2010). Oropharyngeal and esophageal candidiasis occur commonly and can often be successfully treated with topical nystatin and/or clotrimazole, though severe cases requiring systemic therapy can occur despite topical prophylaxis. However, it is the risk of invasive candidiasis especially in the first 3 months post-pancreas transplantation that significantly contributes to morbidity and mortality, and universal prophylaxis with fluconazole during this time period is commonly employed. Common sites of invasive candidiasis include the bloodstream, SSIs, and urinary tract (Pappas et al. 2010). Intra-abdominal and wound infections are the most frequent manifestations of invasive candidiasis, and these infections are often mixed with bacterial pathogens (Lumbreras et al. 1995). Five species of *Candida* (*C. albicans*, *C. glabrata*, *C. tropicalis*, *C. parapsilosis*, and *C. krusei*) account for 90% of invasive disease in humans. *C. albicans*

accounts for roughly 50% of isolates (Silveira et al. 2013), but the more widespread use of azoles such as fluconazole has led to a higher incidence of resistant *Candida* species such as *C. glabrata* and *C. krusei*. Well-known risk factors for invasive candidiasis include age, central venous catheterization, use of total parenteral nutrition, prolonged ICU stay, prolonged neutropenia, diabetes mellitus, and renal replacement therapy. Among pancreas transplant recipients, enteric drainage is associated with a higher risk of invasive candidiasis than bladder drainage. Other identified risks include vascular thrombosis, post-perfusion pancreatitis, acute renal failure, recent CMV infection, primary graft failure, early surgical re-exploration, and early colonization with *Candida* species (Benedetti et al. 1996; Marik 2006).

Definitive diagnosis of invasive candidiasis requires isolation of *Candida* species from a sterile body site. Blood cultures are relatively insensitive, with an overall sensitivity of approximately 50% (Clancy and Nguyen 2013) and slow turnaround times. Tissue cultures have a similarly low sensitivity, and specimen collection may require invasive procedures. Newer techniques for diagnosis include PCR and antigen testing. Currently, serum 1,3-β D-glucan is the most reliable and widely used non-culture method. 1,3-β-D-glucan is a component of the cell wall of *Candida* species as well as *Aspergillus*, pneumocystis, and many other fungal species. Commercial 1,3-β-D-glucan serum assays have been developed and approved as an adjunct to routine cultures for the diagnosis of invasive fungal infections. Although not specific for invasive candidiasis (sensitivity 75–80%, specificity 80%), these assays can identify invasive candidiasis days to weeks prior to cultures and decrease the time to initiation of appropriate fungal therapy (Ostrosky-Zeichner et al. 2005). Antifungal therapy may decrease the sensitivity of these assays, and false positives may occur with other systemic infections, hemodialysis with cellulose membranes, receipt of immunoglobulin, intravenous amoxicillin-clavulanate, and mucositis. Nevertheless, 1,3-β-D-glucan may still be useful in the context of serial evaluation to trend consecutive values in the context of monitoring clinical course or response to therapy. PCR techniques including T2 magnetic resonance have higher sensitivity and specificity and can provide species level identification and information on markers of drug resistance, but more data is still needed to define the role of these techniques in early diagnosis.

Recently updated guidelines on the management of invasive candidiasis have shifted to the use of echinocandins as initial empiric therapy in cases of candidemia or intra-abdominal infections. Fluconazole can still be used as an alternative initial therapy in patients who are not critically ill or considered unlikely to have fluconazole-resistant *Candida* species (Pappas et al. CID 2016). Antifungal susceptibility testing, including routine testing for azole susceptibility in blood and other clinically relevant isolates, is recommended as is testing for echinocandin resistance in cases of C. glabrata or C. parapsilosis. Central venous catheters should be removed promptly in cases of candidemia, and IDSA and ATS guidelines recommend that all non-neutropenic patients should have dilated ophthalmologic exam within the first week. Dilated eye exam in neutropenic patients should be deferred until resolution of neutropenia as ocular findings may not be apparent until counts recover. Blood cultures should be repeated daily or every other day in cases of candidemia to document clearance, and treatment should continue for at least 2 weeks after negative blood cultures and resolution of attributed symptoms if no obvious metastatic focus. Treatment of intra-abdominal candidiasis should include appropriate drainage and debridement, with duration of antifungal therapy dependent on source control and clinical response.

The incidence of invasive aspergillosis (IA) in pancreas transplantation has not been specifically defined but is lower than in heart, lung, and liver transplants. Data from renal transplants which may better reflect the risk in SPK show a rate of 0.7–4% and is associated with prolonged and high doses of steroids as well as graft failure, requiring intensification of immunosuppression and hemodialysis (Singh et al. 2013). Local wound infections can occur, but IA is typically acquired from inhalation of conidia from the environment and

frequently manifests as either localized (pulmonary or extrapulmonary) or disseminated disease. Similarly, Zygomycetes (*Mucor* and *Rhizopus*) are soil pathogens acquired from inhalation that can cause invasive rhinocerebral disease, atypical pulmonary infection, or disseminated disease in poorly controlled diabetics or immunocompromised populations.

Cryptococcus neoformans is reported to account for 8% of invasive fungal infections in solid organ transplant recipients (Baddley et al. 2013). Occurrence is typically late, with a median time of onset of 16–21 months posttransplantation (Husain et al. 2001). *Cryptococcus* is acquired from inhalation of the organism from soil or bird droppings. The majority of cases posttransplant represent reactivation rather than primary infection, but donor-derived cases have also been reported. Cryptococcosis presents commonly as central nervous system or pulmonary disease (often manifesting as nodules, effusions, or consolidations), but cutaneous disease and involvement of other organs (liver, kidneys, etc.) can also occur. Approximately 50–75% of SOT recipients with cryptococcosis have extrapulmonary or CNS disease. All SOT recipients with cryptococcal infection should undergo lumbar puncture, as therapy for CNS disease requires a more intensive antifungal treatment regimen (Perfect et al. 2010).

The risk of endemic mycoses such as histoplasmosis, blastomycosis, and coccidioidomycosis varies with geographic distribution and travel exposures, with donor-derived infections also reported. The estimated incidence of endemic mycosis in SOT recipients is <5% (Miller et al. 2013). Symptomatic disease can occur from primary infection secondary to exposure to pathogen in the environment or from reactivated disease. Infections can be isolated to pulmonary or cutaneous infections or present as disseminated disease.

The use of routine PJP prophylaxis and steroid-sparing immunosuppressant regimens has decreased the incidence of PJP pneumonia in SOT recipients. However, PJP should continue to be part of the differential for respiratory illnesses in patients who have been noncompliant or unable to take prophylaxis, or in whom prophylaxis has been discontinued who then require increased immunosuppression. Risk factors for PJP include corticosteroid therapy at doses equivalent to ≥20 mg of prednisone for at least month, antilymphocyte antibodies (alemtuzumab conferring highest risk), CMV disease, allograft rejection, CD4+ T cells <200, prolonged neutropenia, and direct contact with infected patients for SOT recipients not receiving prophylaxis (Martin et al. 2013). Signs and symptoms include marked hypoxemia, dyspnea, nonproductive cough, fever, or chest pain, usually in the absence of significant physical or radiological findings. CXRs may be normal or show diffuse bilateral interstitial infiltrates; CT may be more sensitive, but there are no pathognomonic radiological findings. Diagnosis involves direct visualization of organisms on respiratory specimens using GMS, Wright, or Giemsa stains. Bronchoalveolar specimens have a sensitivity of approximately 70%; the yield is higher with transbronchial lung biopsy. Given the lower burden of organisms in transplant recipients compared to HIV patients, routine sputum and induced sputum specimens generally have a yield of less than 50%. Use of PCR on respiratory specimens adds variable sensitivity and specificity depending on the type of specimen (routine sputum vs. BAL). Measurement of 1,3-β-D-glucan has sensitivity of >95%, but specificity is only in the mid-80s. TMP-SMX is the most effective systemic therapy and remains a first-line treatment for PJP. Pentamidine can be substituted as second-line treatment for severe disease but carries the risk of islet cell necrosis and pancreatitis. Atovaquone or primaquine/clindamycin is only indicated for mild to moderate cases. Duration of treatment is typically 14–21 days, and adjunctive steroids should be administered when PaO2 is less than 70 (ideally within 72 h of starting PJP treatment).

Parasitic

Increasing immigration, international travel, and transplantation in endemic countries have increased the frequency of parasitic infections seen posttransplant (Schwartz et al. 2013).

A wide variety of parasites may cause disease secondary to either reactivation of latent infection or naturally acquired or donor-transmitted primary infection, but the most common pathogens include *Toxoplasma gondii*, *Trypanosoma cruzi*, and *Strongyloides stercoralis*.

Toxoplasmosis may be secondary to primary infection from contaminated food or water or infected allograft, or reactivation of latent infection. Risk factors for toxoplasmosis include ingestion of cysts in undercooked meat or contaminated soil, contact with oocysts in cat feces, maternal transmission, blood transfusion, or SOT (Kotton 2007). Clinical manifestations can include fever, myocarditis, lymphadenopathy, hepatosplenomegaly, meningitis, brain abscess, pneumonia, hepatitis, or disseminated disease. Although the incidence of toxoplasmosis has decreased significantly with the use of TMP-SMX prophylaxis, disease less often manifests in the first 3 months posttransplant, but later cases after discontinuation of prophylaxis occur (Fernandez-Sabe et al. 2012). CNS toxoplasmosis appears on radiographic imaging as multiple ring-enhancing lesions, and CSF may have a mononuclear CSF pleocytosis and increased protein. In the appropriate clinical setting with elevated serum IgG, empiric therapy may be considered.

Trypanosoma cruzi, the etiologic agent of Chagas' disease, is transmitted by the triatomine insect vector in endemic Latin American countries. Acute disease usually presents as nonspecific constitutional symptoms, facial or lower extremity edema, local skin manifestations at the site of the insect bite (chagoma), lymphadenopathy, hepatosplenomegaly, or rarely acute myocarditis or meningitis. Chronic infection may manifest after many years as cardiomyopathy, megaesophagus, megacolon, and irreversible peripheral nerve changes. Disease can occur through reactivation of latent disease or donor-derived transmission, which is most common in cardiac transplantation with undefined rates in other types of organ transplantation. Reactivation is most commonly described in the first year posttransplant; parasitemia may be asymptomatic, but skin lesions and cerebral mass lesions, which are uncommon in immunocompetent hosts, can occur (Bern 2012). Diagnosis is usually through PCR of blood or infected tissue and evaluation of peripheral smear for parasitemia; chronic infection status is confirmed through serological testing.

Strongyloidiasis has been well characterized in SOT recipients, either due to reactivation of latent disease or donor-derived infection. It can manifest as acute infection, chronic infection, or hyperinfection and disseminated disease. Acute infection can manifest as rash, pulmonary symptoms with eosinophilia, diarrhea, and abdominal pain. Chronic infection is commonly asymptomatic but may cause isolated fluctuating eosinophilia or recurrent rashes. The development of hyperinfection syndrome and disseminated disease is linked to level of immunosuppression and is thus more common in transplant recipients than the general population. Risk factors include corticosteroid therapy, other immunosuppressive agents, HTLV-1 coinfection, and DM (Mejia and Nutman 2012). Mortality rates in untreated transplant recipients can reach 50% in hyperinfection syndrome and 70% in disseminated infection (Patel et al. 2008). Hyperinfection is secondary to increased number of larvae in the lungs and intestines, and disseminated disease can affect additional organs such as the CNS, kidneys, or liver. Clinical manifestations include bloody diarrhea, intestinal obstruction or ileus, peritonitis, intestinal ulceration, pneumonitis with diffuse interstitial infiltrates or consolidation, linear rashes, and sepsis or bacterial meningitis with gram-negative bacteremia. Eosinophilia is usually absent in hyperinfection and disseminated disease. Diagnostic methods include serological testing, examination of the stool, sample of duodenal fluid or small bowel biopsy, or examination of other affected body fluids and tissues. Pretransplant evaluation should include combination of serology and stool examination, and recipients and donors from endemic areas or with unexplained eosinophilia should be screened (Schwartz et al. 2013). Patients with confirmed *Strongyloides* should also be tested for HTLV-1 coinfection, as such cases typically require more protracted therapy. The drug of choice for both severe and uncomplicated disease is ivermectin; albendazole is an alternative second-line treatment (Schwartz et al. 2013).

Pretransplant Screening

Pretransplant screening of organ donors and recipients is essential to (1) identify any infectious conditions in either the donor/recipient that may preclude transplantation, (2) diagnose and treat any active infections prior to transplantation, (3) help stratify infection risk, and (4) design antimicrobial prophylaxis and vaccination strategies to reduce the risk of infection. Guidelines for pretransplant infection screening in both organ donors and recipients for major infections have been developed (Fischer et al. 2013). These must be individualized for other known transmissible infections based on exposure and medical history. The extent of screening may vary among transplant centers, and the risk of infection must also always be balanced with the urgency of transplantation as well as the consequences associated with forgoing transplantation. Screening involves serological testing and microbiologic cultures. Nucleic acid testing (NAT) and molecular testing, which may provide earlier identification of some infections in donors, are now more widely available but are not uniformly used.

Donor

The Organ Procurement and Transplant Network (OPTN) has established minimum criteria for testing of potential pancreas donors. In individual cases, where a potential acute bacterial infection may impact the suitability of an organ for transplant, discussion with the transplant infectious disease consultant is essential, both in making the final decision on whether to accept the donation and in crafting a preemptive antimicrobial strategy for the recipient.

Recipient

The goal of screening potential organ recipients is to diagnose and treat any active infections prior to transplantation, identify chronic viral pathogens or pathogens at risk for reactivation with posttransplant immunosuppression, and design appropriate perioperative and posttransplant antimicrobial prophylaxis. In addition to standard serological testing, a thorough medical history especially in regard to prior infections, history of resistant pathogens and past treatments, and epidemiologic exposures should be elicited to help guide additional testing/prophylaxis. Routine screening for recipients includes serological testing for HIV, CMV, VZV, HSV, EBV, syphilis, hepatitis B, and hepatitis C. All transplant recipients should have a PPD or interferon gamma release assay to rule out latent TB and imaging to evaluate for active TB if positive; any active infection should be treated with documented microbiologic and radiologic cure. Although most cases of endemic mycoses in the transplant population are secondary to reactivation of disease, pretransplant evaluation in high prevalence areas is recommended. Incorporating a travel and prior residence history is essential. Patients from, or with prolonged travel to, areas endemic for parasitic infections (tropical countries and southeastern USA) should be undergo serologic testing for *Strongyloides*, HTLV, and *Trypanosoma cruzi*. In many centers, this screening is done in collaboration with Transplant Infectious Diseases.

Prevention of Infection

Strategies to prevent infection include antimicrobial prophylaxis and vaccination but also should include lifestyle counseling (including, but not limited to, hand hygiene, food preparation, avoidance of exposures, and vaccination of family members). Antimicrobial prophylaxis has significantly altered the pattern of posttransplant infections including the incidence, severity, and timing. However, there are no consensus guidelines on prophylaxis post-pancreas transplantation, and antimicrobial prophylaxis practices vary among transplant centers. Nevertheless, many of the principles of prophylaxis post-pancreas transplantation remain the same as other solid organ transplants. In general, antimicrobial prophylaxis can be either universal or preemptive.

Antimicrobial Prophylaxis

Antimicrobial prophylaxis depends on host and donor epidemiologic factors/screening as well as the presence of technical complications and the type of immunosuppression used. These factors must constantly be assessed to determine the patient's risk of infection and accordingly prescribe prophylaxis, if available.

Routine surgical prophylaxis varies by transplant center but should include coverage for enteric and fungal organisms in addition to gram-positive coverage. As with other surgical procedures, the first dose of antibiotic is administered 30–60 min prior to the incision and continued for 24 h post procedure. Prophylaxis should be modified and individualized for each patient based on their epidemiologic history/prior exposures and known colonization patterns with resistant organisms such as MRSA or VRE.

Trimethoprim-sulfamethoxazole (TMP-SMX) is commonly used for PJP prophylaxis and also provides coverage for *Toxoplasma*, *Listeria*, many *Nocardia* species, *Isospora*, and *Cyclospora* as well as many common causes of urinary and respiratory infections. In cases where TMP-SMX cannot be used, dapsone or atovaquone can be substituted for PJP prophylaxis but do not provide protection for most of the other organisms listed above (Rodriguez and Fishman 2004). Most transplant centers use TMP-SMX prophylaxis for at least 6 months posttransplant, but evidence on the optimal duration is unclear.

Antifungal prophylaxis is recommended to commence within 7–14 days of transplant and be continued for up to 3 months posttransplant. The highest risk for fungal infection post-pancreas transplantation is in the first 3 months. Fluconazole is the antifungal of choice. However, drug-drug interactions occur with many immunosuppressants, and immunosuppressant levels need to be closely monitored. Echinocandins, amphotericin, and other azoles are usually not recommended unless there is a history of resistant *Candida* species or *Aspergillus* or if use of fluconazole is precluded.

Prophylaxis against the herpes family of viruses includes antiviral agents with activity against herpes simplex, varicella-zoster, and cytomegalovirus. The approach to antiviral prophylaxis depends largely on the CMV status of both the donor and recipient. CMV infection is relatively common in pancreas transplantation, and the use of antilymphocyte-depleting antibodies during induction requires extended prophylaxis or monitoring. Both preemptive strategies using weekly CMV PCR as the trigger for initiation of therapy and universal prophylaxis reduce the risk of end-organ CMV disease (Kalil et al. 2005). Some studies have demonstrated that prevention of CMV reduces the incidence of acute and late rejection in organ transplantation. The highest-risk subgroup includes (D+/R-) transplants followed by (D-/R+), with the lowest risk in (D-/R-).

Generally in cases of D+/R-, the recipient receives CMV prophylaxis for 3 months followed by preemptive strategy. In D-/R+ prophylaxis is continued for 3 months. All D+ or R+ patients receiving immunosuppression with antilymphocyte globulin or high-dose steroids should remain on prophylaxis for an additional 3 months. In some centers, D-/R- cases receive acyclovir or famciclovir for the first 3 months. Several randomized clinical trials have shown that ganciclovir-based prophylaxis (IV ganciclovir or PO valganciclovir) is superior to acyclovir-based prophylaxis in prevention of reactivation and primary CMV disease in solid organ transplantation (Rubin et al. 2000; Flechner et al. 1998; Winston et al. 1995). Universal antiviral prophylaxis also helps to prevent HSV, VZV, EBV, and HHV 6 and 7, in addition to indirectly reducing the higher risk of associated fungal and bacterial coinfection with CMV (Fishman 2007). It must be kept in mind that the risks of drug-induced bone marrow suppression and other side effects increase with longer courses of prophylaxis.

Vaccinations

Vaccination history constitutes an important part of the pretransplant evaluation as well as approach to prophylaxis. Transplant candidates and their household members should be up to date with

vaccinations, which should be completed pretransplantation whenever possible to avoid the possible risk of disseminated disease from live vaccine strains in immunocompromised recipients and to optimize the efficacy of the immunization (Kumar et al. 2007). Most transplant centers resume immunization of recipients at 3–6 months posttransplantation or when baseline immunosuppression levels are achieved. The schedules for both pre- and posttransplant immunizations are standardized (Danziger-Isakov et al. 2013).

Conclusion

Advances in operative techniques, immunosuppression, and the use of antimicrobial prophylaxis have dramatically changed the classic framework for infection in pancreas transplantation. The risk of infection varies with time posttransplantation and is a complex interplay of underlying host and donor characteristics, epidemiologic exposures, operative factors, and intensity of immunosuppression that must always be balanced with the risk of allograft rejection. Timely diagnosis and therapy of the wide range of infections in this immunocompromised patient population is essential to mitigate the associated morbidity and mortality. A collaborative approach involving infectious disease specialists, the transplant team, and the patient is essential to improved clinical outcomes and survival in pancreas transplantation.

Cross-References

- ▶ Donor Evaluation and Procurement
- ▶ Surgical Complications of Pancreas Transplant

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Islet Cell Transplant

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Abstract

Exogenous insulin administration is currently the only treatment available for patients with type 1 diabetes, but it is not a cure. Long-term complications associated with the disease may be preventable with a treatment strategy that can provide better blood glucose control. The transplantation of isolated islets provides the potential to restore endogenous insulin production and reestablish normoglycemia. Significant progress has been made in the outcomes of clinical islet transplantation, reflecting improvements in nondiabetogenic immunosuppression and preparation of sufficient quantities of highly viable islets for transplantation. Islet transplantation represents a potential cure for patients with type 1 diabetes.

Keywords

Chronic pancreatitis · Collagenase · Diabetes · Insulin · Islet · Islet isolation · Pancreas · Transplantation · Xenotransplantation

Introduction

Diabetes is a tremendous medical burden. It currently affects more than 200 million people worldwide and is projected to affect 5% of the world population by 2030 (Disease Control and Prevention 2014). The most severe form of this disease, type 1 diabetes mellitus (T1DM), represents approximately 10% of all cases of diabetes (Onkamo et al. 1999; Wild et al. 2004).

T1DM, known as insulin-dependent diabetes or juvenile diabetes, is a chronic condition in which beta cells produce little or no insulin. T1DM results from an autoimmune-mediated destruction of insulin-producing beta cells in the islets of Langerhans of the pancreas. In T1DM, the lack of endogenous insulin production leads to hyperglycemia and ketoacidosis unless it is balanced by multiple exogenous insulin injections, which remain the primary treatment for T1DM together with regular monitoring of blood glucose levels (Onkamo et al. 1999; Wild et al. 2004).

T1DM patients develop micro- and macrovascular complications (Vasudevan et al. 2006; Panero et al. 2009). Frequent daily injections of exogenous insulin and tight control of blood glucose delay progression of microvascular diseases, including retinopathy and neuropathy, but do not entirely prevent these complications (Agarwal and Brayman 2012). Regular exogenous insulin treatment does not restore a normal glucose level all the time. Maintaining a stable glucose level is highly important for preventing the development of secondary complications (Rao and Morghom 1990). The mortality and morbidity related to poor blood glucose control have been studied by the Diabetes Control and Complication Trial (1993, 1994; Fahrmann et al. 2015) and the UK Prospective Diabetes Study (1998). These reports demonstrated the need for maintaining normal

physiological euglycemia to prevent and control the progression of microvascular and macrovascular complications. T1DM presents a substantial burden upon patients' quality of life, especially for children and adolescents (Centers for American Diabetes Association 2014).

Despite exogenous insulin therapy, normal physiological glycemic control can only be achieved by restoring in vivo insulin secretion from the beta cells of the islets of Langerhans (Oberholzer et al. 2003; Ichii and Ricordi 2009; Matsumoto 2011; Bruni et al. 2014). Replacement of pancreatic islet cells is, hypothetically, an ideal treatment for patients with T1DM (Sutherland et al. 2004). This treatment functions to restore endogenous insulin secretion to a diabetic patient by offering the functioning beta cells lost from the recipient's native pancreas. Some of the most difficult cases of T1DM include patients who lost their ability to feel hypoglycemic prodromic symptoms such as sweating, tremor, tachycardia, and anxiety (Ichii and Ricordi 2009). Since it is very challenging and potentially dangerous to treat these subjects with intensive insulin therapy, transplantation of insulin-producing cells could be of assistance in restoring proper glucose regulation (Jun 2010).

Beta cell replacement to diabetic patients can be achieved by either whole-organ pancreas transplantation (Vrochides et al. 2009) or isolated islet cell transplantation (Kandaswamy and Sutherland 2006; Vrochides et al. 2009). Implantation of a whole pancreas requires a major surgical procedure and presents complications related to the excessive exocrine drainage of the implanted pancreas (Kandaswamy and Sutherland 2006; Sa et al. 2008). Simultaneous pancreas and kidney transplantation is presently considered standard therapy for patients with T1DM with end-stage renal failure (Redfield et al. 2015). Although pancreas transplantation offers some advantages (including long-term stable normoglycemia), especially when the pancreas is associated with a kidney graft in uremic diabetic patients, the procedure entails considerable risks to the recipient (Sutherland 2003). Islet cell transplantation is not a major surgical procedure; it can be performed with the help of a trained interventional radiologist on an outpatient basis and can be repeated several times without major discomfort to the patient (Bruni et al. 2014). Achieving normal blood glucose by means of islet transplantation improves quality of life and ameliorates secondary diabetic complications (Bottino et al. 2002b).

This chapter begins by reviewing the history of islet transplantation. It then outlines the steps involved in islet allotransplantation and discusses care of the islet transplant recipient. The final sections review the outcomes of islet transplantation, its challenges, and alternative sources of beta cells.

History of Islet Transplantation

The introduction of insulin therapy in 1922 by Frederick Banting and Charles Best revolutionized the treatment of patients with diabetes and prolonged the lives of millions of people (Banting et al. 1922; Polonsky 2012). While insulin therapy treats patients with diabetes, however, it does not cure the disease nor does it prevent the development of the secondary complications associated with long-term diabetes. The need for a more permanent cure spurred researchers to explore other options. The pioneering experiments of Lacy and Kostianovsky in 1967 (Lacy and Kostianovsky 1967) showed that viable islets could be extracted from the pancreas of a rodent donor and reinfused in the portal vein of a diabetic rat recipient to achieve stable euglycemia (Lacy and Kostianovsky 1967). These experiments provided the basis for the emergence of islet isolation and transplantation. Subsequent discoveries related to enzymatic digestion and tissue purification paved the way for successful large-scale human islet isolation. The intraductal injection of collagenase proved an effective method for successful islet isolation from large animals and humans (Lakey et al. 2003).

The first clinical islet transplant was performed at the University of Minnesota by Dr. John S. Najarian and Dr. David E. R. Sutherland (Najarian et al. 1977). Early islet transplants had very little success, as it was difficult to obtain sufficient amounts of human islets for

allotransplantation until a new method for the isolation of human islets from the pancreas was described by Dr. Camillo Ricordi (Ricordi et al. 1988). This new approach allowed the extraction of consistently high numbers of purified and viable human islets for transplant. In subsequent years, attempts at transplanting islets into diabetic recipients were rather unsuccessful, except for the cases described in the early 1990s in Pittsburgh of patients with surgical rather than autoimmune diabetes who received multiorgan transplants, including islets. This first successful series of islet allografts provided the proof of concept. Despite these efforts, only 8% of all diabetic recipients of islet grafts worldwide could maintain free of exogenous insulin (Carroll et al. 1992).

In 2000, researchers at the University of Alberta in Edmonton, Canada, reported successful reversal of diabetes in seven consecutive patients by pancreatic islet transplantation (Shapiro et al. 2000). Their novel immunosuppressive regimen with meticulous preparation of islets, later named the "Edmonton protocol," revolutionized the field of islet transplantation. This protocol used improved techniques in pancreas procurement and isolation, with a focus on transplanting an adequate islet mass and using corticosteroid-sparing immunosuppression (Shapiro et al. 2006). Specifically, the protocol involved harvesting the pancreas prior to multiorgan retrieval; avoiding prolonged cold storage of the pancreas, processing the pancreas for islet isolation immediately; avoiding animal serum products during isolation; infusing an islet mass of greater than 10,000 islet equivalents (IEQ)/kg of recipient body weight by infusing islets from two to three donors; and using an immunosuppressive protocol comprising induction therapy with a humanized interleukin-2 receptor antibody (daclizumab) and maintenance therapy comprising low-dose tacrolimus and sirolimus (Shapiro et al. 2000).

The international trial of the Edmonton protocol for islet transplantation was organized by the Immune Tolerance Network and was initiated by the National Institutes of Health in order to establish centers of excellence to conduct tolerance-based trials (Shapiro et al. 2006). The trial consisted of a series of 36 T1DM subjects across nine international islet centers who received islet transplants. Islets were isolated from the pancreases of deceased donors and were transplanted after purification, without any culture period. The study results showed that 21 subjects (58%) attained insulin independence with stable glycemic control at any point throughout the trial. Of these subjects, 16 (76%) required insulin again at 2 years; 5 of the 16 subjects (31%) who reached the primary endpoint remained insulin independent at 2 years (Shapiro et al. 2006). Following the trial, high rates of insulin independence were observed 1 year posttransplant in leading islet transplant centers, and an international multicenter trial demonstrated the reproducible success of the approach. In the centers with the most experience with the procedure, approximately 80% of patients treated with islet transplantation could achieve insulin independence within the first year posttransplantation (Shapiro et al. 2005).

A series of major clinical trials have been performed by the Clinical Islet Transplant (CIT) Consortium (CIT website: http://www.citislet study.org/) (Clinical Islet Transplant Study 2014). This consortium is a network of clinical centers and a data coordinating center established in 2004 to conduct studies of islet transplantation in patients with T1DM. Studies conducted by the CIT Consortium are focused on improving the safety and long-term success of methods for transplanting islets (2014). Seven CIT clinical trials have been completed or are nearing completion, including two phase 3 clinical trials underway to support the biological license application mandate from the US Food and Drug Administration (FDA): (2014)

- CIT-01: Open randomized multicenter study to evaluate the safety and efficacy of low-molecular-weight sulfated dextran in islet transplantation (Nordic countries)
- CIT-02: Strategies to improve long-term islet graft survival (University of Miami and University of Illinois, Chicago)
- CIT-03: Peritransplant deoxyspergualin in islet transplantation in T1DM (University of California-San Francisco, University of Minnesota, and Northwestern University)

- CIT-04: Islet transplantation in T1DM with LEA29Y (belatacept) maintenance therapy (University of Alberta and Emory University)
- CIT-05: B lymphocyte immunotherapy in islet transplantation: toward calcineurin inhibitor–free immunosuppression (University of Pennsylvania)
- CIT-06: Islet transplantation in T1DM kidney allograft recipients: efficacy of islet after kidney transplantation (all North American sites)
- CIT-07: Islet transplantation in T1DM (all North American sites) (Phase III clinical trial for obtaining biological licensure)

The results of these clinical trials will be available to public in near future (CIT website: http://www.citisletstudy.org/).

As of 2014, over 750 islet allotransplants have been performed across more than 30 international islet processing facilities (Fig. 1). A recent report from the Collaborative Islet Transplant Registry (Balamurugan et al. 2014c) stated that 44% of islet allotransplant recipients were insulin independent 3 years after receiving an islet graft from 2007 to 2010 (Bruni et al. 2014). However, few islet processing facilities perform islet allotransplants in the USA because of the treatment's classification as an experimental therapy and not a clinical therapy. As a result, acquiring sufficient funding to continuously perform islet allotransplants has proven difficult. Islet facilities in other countries, most notably in Europe, are not subject to the FDA and have established clinical islet transplant programs. The University of Alberta (Canada) is currently the most active center, having performed 66 islet transplants in the year 2013 alone (Barton et al. 2012). The Edmonton group has reported that after 400 islet preparations in over 200 patients, 79% of recipients showed full or partial graft function (Bruni et al. 2014).

Islet Allotransplant Procedure

The islet allotransplantation procedure must be conducted in an approved facility. Initial steps in the procedure include donor selection, pancreas procurement and preservation, islet isolation, islet purification and culture, islet quality assessment, and recipient selection and preparation. Transplantation involves infusion of cultured islet cells into the portal vein of the recipient's liver.

Dedicated Cleanroom Facility

The islet isolation procedure is highly specialized and requires a team of trained processing specialists in a dedicated current good manufacturing practice (cGMP) cleanroom facility. These facilities require daily monitoring of temperature, relative humidity, and pressure differential to ensure optimal conditions for islet processing. In addition, strict disinfection protocols must be followed to maintain acceptable levels of microorganism presence. Prior to entering the processing area, the islet processing staff must don sterile clothing over clean scrubs to avoid transporting outside contaminants. Sterile technique is used throughout the isolation procedure and during any facility disinfection or maintenance (Balamurugan et al. 2014b).

Pancreas Donation and Procurement

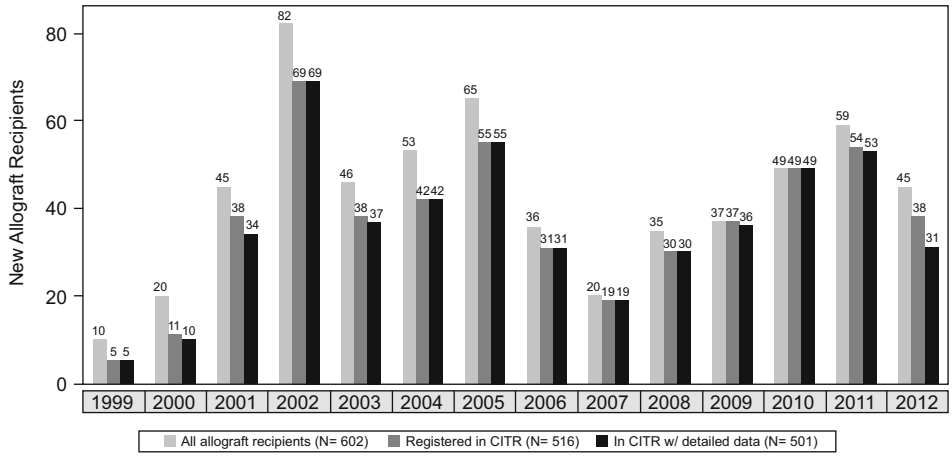
Cadaveric donor pancreases are procured by a trained surgeon. The recovery, purification, and functionality of isolated islets will depend upon the procurement method and care of the pancreas (Lakey et al. 2002). Donor pancreases are allocated according to well-established criteria determined by the United Network for Organ Sharing (UNOS), a private, nonprofit organization under government contract to operate the national organ matching registry, or the Organ Procurement and Transplantation Network (Berney et al. 2005). UNOS uses an algorithm to match donors with the most suitable candidates based on recipient characteristics and works with local organ procurement organizations to allocate donor organs (Berney et al. 2005; Berney and Johnson 2010). Donor pancreases are selected based on donor characteristics including age, body mass index, medical history, social history, biochemical parameters, and cardiac arrest downtime (Balamurugan et al. 2014c).

Pancreas Preservation and Transportation

Ischemia to the pancreas during either procurement (warm ischemia) or storage (cold ischemia) is associated with functional impairment of islets (Noguchi 2011). In general, the standard organ procurement procedure minimizes warm ischemia. However, cold storage occurs during transport of the pancreas to the islet lab and preparation of patients for transplantation. Prolonged cold storage of the pancreas leads to adverse

Exhibit 1 – 4A

Total Number of Islet Allograft Recipients, Recipients at CITR-Participating Centers, and Recipients with Detailed Data Reported to CITR by Year of First Islet Allograft Infusion: Allograft recipients at North American Islet Transplant Centers 1999-2012

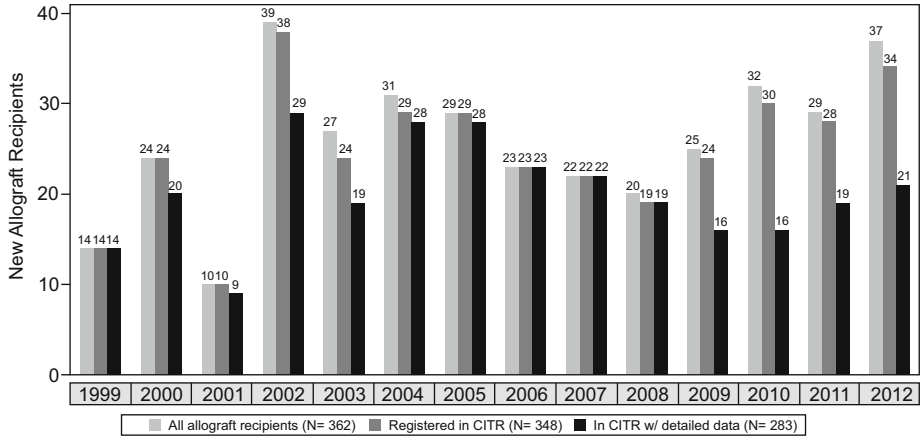


CITR Data 17Dec2013

From 1999-2012, 602 patients with type 1 diabetes mellitus received at least one islet allograft infusion procedure in North America. Of these, 516 (85.7%)) consented to and were registered in CITR. Detailed data was available on 501 of these recipients, representing 83.2% of the overall 602.

Exhibit 1 – 4B

Total Number of Islet Allograft Recipients, Recipients at CITR-Participating Centers, and Recipients with Detailed Data Reported to CITR by Year of First Islet Allograft Infusion: Allograft recipients at CITR-Participating European and Australian JDRF Centers 1999-2012

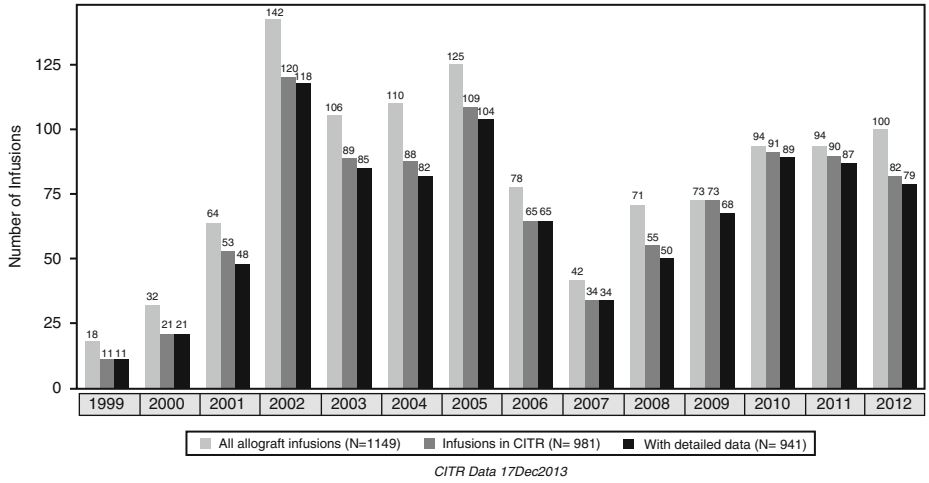


CITR Data 17Dec2013

Fig. 1 (continued)

Exhibit 1–5A

Total Number of Islet Allograft Infusion Procedures Performed and Number with Data Reported to CITR: CITR-Participating North American Islet Transplant Centers 1999-2012



From 1999-2012, 601 North American islet transplant recipients of allograft islets received a total of 1,149 infusion procedures. CITR-participating centers reported 981 (85.4%) of those procedures. The Registry has received detailed data relative to 941 of those procedures, representing 81.9% of all 1,149 infusions.

Exhibit 1–5B

Total Number of Islet Allograft Infusion Procedures Performed and Number with Data Reported to CITR: CITR-Participating European and Australian JDRF Centers 1999-2012

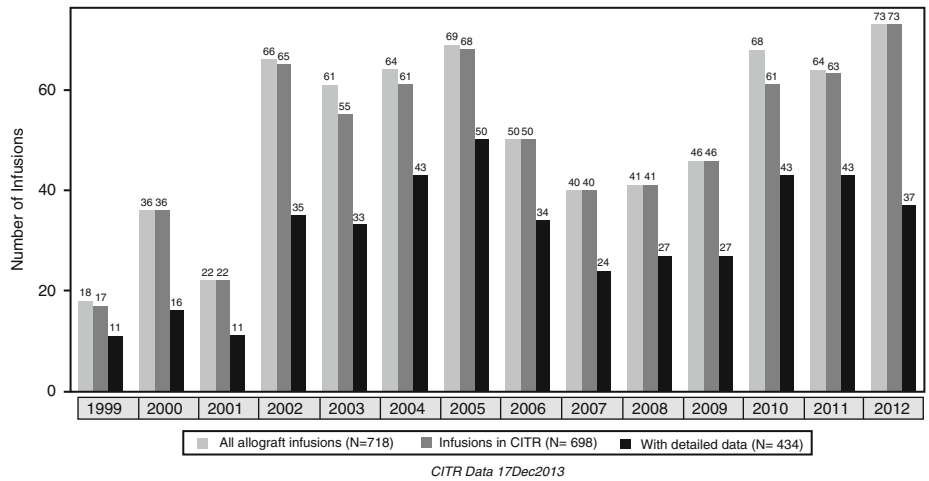


Fig. 1 Collaborative Islet Transplant Registry data show the number of islet transplantation performed worldwide

biochemical events and is unfavorable to islets (Guibert et al. 2011). Decreased islet yield is associated with the degree of cold ischemia of the pancreas.

The two-layer method (TLM) of pancreas preservation using perfluorocarbons (PFC) and University of Wisconsin (UW) solution is a special practice to provide oxygenation of the pancreas during transportation (Fujino 2010). PFC, which stores and releases high levels of oxygen, has been used in organ preservation (Matsumoto 2005). PFC-based preservation before islet

isolation and transplantation was introduced into clinical practice by the University of Minnesota group (Hering et al. 2002). Kuroda et al. (Tanaka et al. 2005) first introduced the TLM of cold storage for vascularized pancreas preservation, and Matsumoto et al. (Matsumoto 2005) reported clinical transplantation of vascularized pancreases after TLM storage. The Edmonton group demonstrated that pancreases preserved in UW solution for prolonged periods (>10 h) can be rescued by an additional 3 h of preservation with the TLM (Tsujimura et al. 2003). Ricordi et al. studied the efficacy of PFC-based preservation on marginal (donor age >50 years) human pancreases (Ricordi et al. 2003). PFC-based preservation has the potential to expand the donor pool by using pancreases with cold ischemia times >10 h, marginalized pancreases from non–heart-beating donors, and pancreases from older donors (age >50 years). Shorter cold storage of pancreases is always beneficial for islet isolation outcomes, but the TLM method is essential when prolonged cold storage is unavoidable. During nonavailability of TLM setup, regular cold storage transport of pancreas is acceptable for clinical islet isolation.

Islet Isolation

The isolation procedure begins when the cadaveric donor pancreas arrives at a designated cleanroom facility. All phases of the procedure are performed inside biosafety cabinets. An initial trim is performed to carefully remove the duodenum, spleen, and peripancreatic fat while maintaining the integrity of the pancreatic capsule (Lakey et al. 2003). The pancreas is then submerged in a povidone iodine solution to disinfect the surface. The main pancreatic duct is cannulated using an intravenous cannula and fixed in place with a suture. A cold enzyme solution, containing collagenase and neutral protease, is perfused through the main pancreatic duct either manually using a syringe or in a semiautomated manner with a peristaltic pump. After the pancreas is sufficiently distended, it is cut into smaller pieces and transferred to the digestion circuit, which is composed of sterile tubing, a heating coil, a heating water bath, a peristaltic pump, and a Ricordi chamber that contains a 500 μm stainless steel filter and 5–6 glass, steel, or silicon nitride marbles to facilitate mechanical dissociation and prevent the pancreas from moving in uniformity with the Ricordi chamber. Phase 1 solution (balanced salt solution) is added to fill the digestion circuit and push all air out of the system. Once the digestion circuit is filled with solution, the enzymatic and mechanical dissociation of the pancreas starts. Then dissociated tissue samples are taken periodically and stained with dithizone, a zinc-binding compound, to monitor the release of free islets. An experienced islet processing specialist determines when the digestion phase ends and the collection of dissociated tissue begins. Tissue is collected in cold media containing human serum albumin to deactivate the enzyme and protect islets from further digestion and fragmentation. The collected tissue is distributed evenly between 250 mL conicals and centrifuged at 140 g. After all of the tissue is collected, it is combined into a single 250 mL conical, and a sample is taken for cell counting. The tissue is washed several times to remove any cellular debris while the purification process is being set up (Lakey et al. 2003; Balamurugan et al. 2014a).

Prior to 1994, crude collagenase was used to isolate pancreatic islets across all species. In 1994, Liberase-HI (Roche Applied Science, Indianapolis, IN) was successfully introduced for use in human islet isolations (Linetsky et al. 1997a; Antonioli et al. 2007). Liberase-HI was the first purified enzyme blend available for worldwide commercial use (Linetsky et al. 1997b). In 2007, Liberase-HI was withdrawn from the market due to concerns of utilizing bovine brain–derived materials in the fermentation process. Following its withdrawal, clinical islet programs were forced to find an alternative enzyme blend (Anazawa et al. 2009). Many enzyme combinations from different companies were tested in different doses in an effort to find a suitable replacement. Collagenases were assessed through collagen-degrading activity and high-performance liquid chromatography to characterize the integrity of collagenases from different suppliers

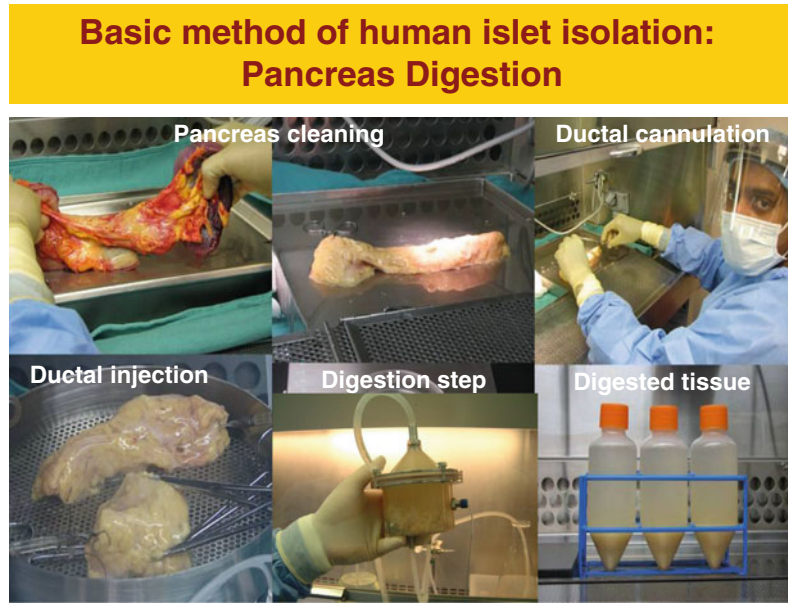


Fig. 2 Basic method of human islet isolation: Pancreas Digestion

(Balamurugan et al. 2010). In 2012, a new enzyme mixture composed of CIzyme collagenase HA (VitaCyte LLC, Indianapolis, IN) was introduced and Neutral Protease NB (SERVA Electrophoresis GmbH, Heidelberg, Germany) to obtain consistently high islet yields in clinical islet allotransplantation and also in clinical islet autotransplantation for patients with chronic pancreatitis(Balamurugan et al. 2012). Recently, a recombinant collagenase was standardized for use in cadaveric donor pancreases for islet isolations performed for discovery research (Balamurugan et al. 2015) (Fig. 2).

Islet Purification

The collected tissue is a mixture of free islets and dissociated exocrine tissue. The purification process aims to separate free islets from the remaining exocrine tissue by centrifuging it in a continuous density gradient made from iodixanol and a cold storage solution. During centrifugation, the less dense islets will rise to the top of the gradient while the more dense acinar cells will gravitate towards the bottom of the gradient. A successful purification does two things: (1) reduces the total transplanted tissue volume and (2) prevents harmful pancreatic enzymes from being cotransplanted with the islets (Loganathan et al. 2011). The continuous gradient is prepared using a magnetic stir plate/magnetic stir bar in combination with a gradient maker (Biorep Technologies, Miami, FL). The gradient and the tissue are loaded into a COBE 2991 cell processor through sterile tubing by way of a peristaltic pump. Once all of the contents are inside the processor, it is centrifuged for 3–5 min. The COBE 2991 dispenses the centrifuged contents using a pneumatic bladder. The contents are collected in twelve 250 mL fractions, and a 200 μL sample from each fraction is taken and visually assessed for purity. The first several fractions should contain free, pure islets, and the later fractions will contain exocrine tissue. Based on the purity, the different fractions are combined individually as pure, middle pure, and low pure for counting (Anazawa et al. 2011).

The CIT Consortium recommends using density ranges of 1.060–1.100 g/cm^3 to prepare the continuous gradient used for islet purification (CIT paper in CellR4). These gradients are used in most clinical isolations. However, a new method was to determine the density distribution of the exocrine and islet tissue from human pancreases prior to the COBE purification process

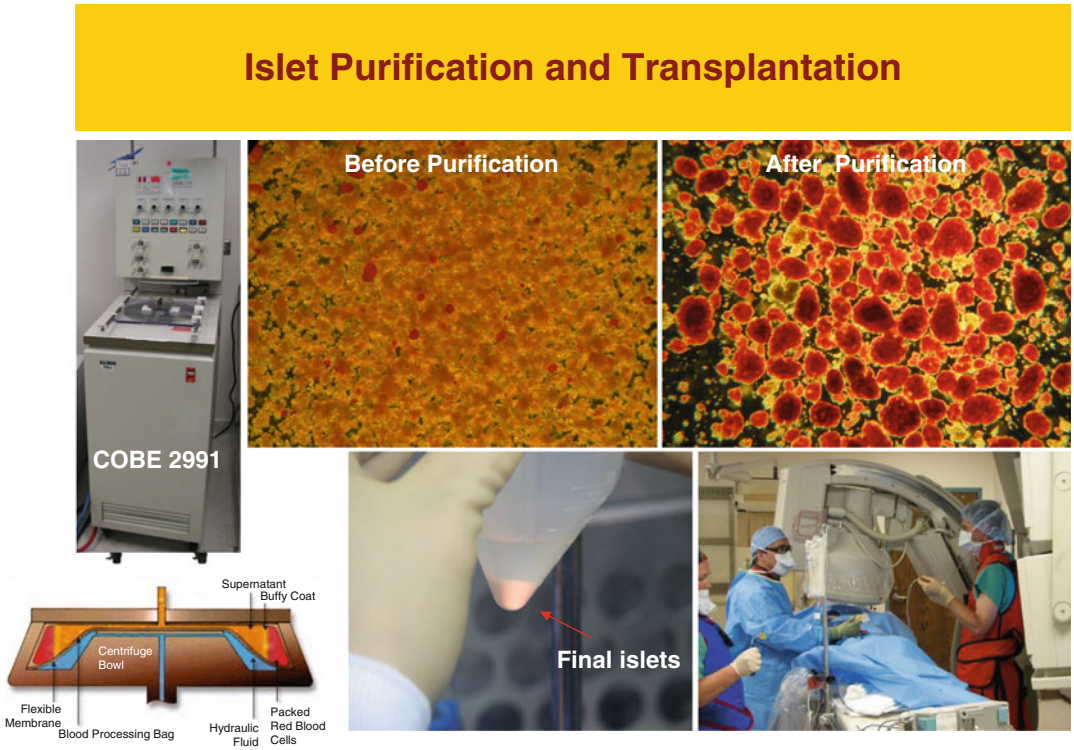


Fig. 3 Islet Purification and Transplantation

using an analytical test gradient system. This system involves taking samples of the pancreatic digest and centrifuging it through a continuous gradient in a single conical tube to determine the peak islet density and the peak exocrine density, which can be used to find the optimal density range for each unique pancreas (Anazawa et al. 2011). In autologous islet preparations, higher range of density gradients (1.075–1.115) was successfully utilized to reduce the pellet size of the pancreatic digest from chronic pancreatitis patients (Anazawa et al. 2011) (Fig. 3).

Islet Culture

After the Edmonton protocol was introduced, islet transplant centers began transplanting islets immediately following purification. However, increasing evidence that islet culture for 36–72 h is beneficial for islet function, despite the possible loss of islet number, has changed standard practice. Islet culture is advantageous in many respects, as it allows time to transport the patients to transplantation centers, allows time to administer prophylactic immunosuppression in islet transplant recipients, provides a substantial opportunity for islet preparation assessment, and may reduce the immunogenicity of the preparation (Froud et al. 2005; Hering et al. 2005).

Assessment of Islet Quality

Treatment of T1DM by transplanting human allogeneic islets is an investigational procedure. In the USA, islet cell transplantation is regulated by the FDA (Linetsky and Ricordi 2008). The FDA requires testing of any cellular and tissue-based product prior to clinical transplantation and demonstration that the product can be safely and reproducibly manufactured. This requirement is generally met by characterizing the product. The lot release for an islet product includes

demonstration of safety (within acceptable limits of fungal, bacterial, pyrogenicity/endotoxin, and any adventitious agents) and assessment of several key product characteristics that include yield, purity, viability, and potency (Papas et al. 2009).

The final supernatant of the islet suspension in the transplant medium is assessed by endotoxin testing and gram stain. The specification for endotoxin is <5 EU/kg. Acceptable gram stains contain no organisms detected within the limit of the assay. After 36–72 h, the cultured cells are pooled and a sample is taken for counting. The minimum islet count for a first transplant is 5,000 IE/kg, and the minimum for a second transplant is 3,000 IE/kg. Islet cell purity, visually assessed by dithizone staining, should be >30%. Islet viability is based on inclusion/exclusion dyes (fluorescein diacetate/propidium iodide) and is assessed visually using fluorescence microscopy. The islet preparation should be >70% viable to be released. Islet potency is assessed by glucose-stimulated insulin release, which should be >1 (Papas et al. 2009).

These specifications are meant to exclude preparations that are contaminated, highly impure, grossly damaged, or contain an insufficient number of islets for transplant. The specifications provide reasonable estimates of islet safety, identity, and purity, but do not have reliable measures for the viability or potency of the preparation. Therefore, the establishment and validation of useful tests for islet viability and potency are urgently needed for meaningful islet preparation assessment prior to transplantation. Establishing reliable viability and potency tests could aid in predicting islet transplantation outcomes (Papas et al. 2009; Bottino and Trucco 2015).

Patient Selection

Although islet transplantation is a safe and minimally invasive procedure, the need for long-term immunosuppression limits the pool of recipients (Bruni et al. 2014). Patients must meet three criteria to become eligible for an islet allotransplant: (1) a history of life-threatening hypoglycemic unawareness, (2) progression of long-term complications of T1DM despite conventional attempts for disease management, and (3) difficulty controlling diabetes despite aggressive medical treatment. Recipients must have also had T1DM for at least 5 years and be between 18 and 65 years of age (McCall and Shapiro 2014).

An estimated 15–20% of T1DM patients experience hypoglycemia unawareness (Pedersen-Bjergaard et al. 2004) – a result of losing the ability to counterregulate the effects of exogenous insulin, resulting in blood glucose levels dropping to dangerously low levels without the warning signs or side effects that normally accompany such an event. For individuals who experience hypoglycemia unawareness, a hypoglycemic episode is life threatening; 7–10% of deaths from T1DM are a direct result of a hypoglycemic episode (Cryer 2005). To improve overall quality of life for patients who experience hypoglycemic episodes, islet allotransplant is believed to have benefits that exceed the risks of a lifetime of immunosuppression therapy.

Another indication for islet allotransplant is microvascular disease as a result of long-term complications of T1DM. Preliminary data from the University of British Columbia suggests a significant reduction in the development of retinopathy and nephropathy in islet recipients compared with patients who rely on daily exogenous insulin therapy (Thompson et al. 2008; Thompson et al. 2011a).

Preparation for Transplant

After the islets have been cultured for 36–72 h and all release criteria have been met, including sterility, viability, and functionality by glucose-stimulated insulin release, the final cultured islet product is suspended in 100 mL of transplant media (CMRL 1066 + human serum albumin + HEPES buffer) and loaded into a 600 mL blood transfusion bag. A total of 70 units per kg/patient body weight of heparin is added to the final product suspension. A second smaller transfusion bag is connected to the product bag and filled with 50 mL of transplant media as a “rinse” bag to push any remaining tissue from the product bag during the infusion (Balamurugan et al. 2014b).

Islet Transplant Procedure

Currently, the most common site of infusion is the portal vein of the liver. This location allows for percutaneous infusion, while the structure of the liver promotes islet engraftment by preventing islets from flowing directly through the bloodstream. Additionally, total intrahepatic blood flow helps maximize islet function. The suspended islets are infused over a period of about 20–40 min. The pressure of the portal vein is monitored throughout infusion to detect any spikes that may occur. A significant rise in pressure requires termination of portal infusion and selection of an alternative transplant site for any remaining product.

Care of the Islet Transplant Recipient

In the period immediately following the transplant, insulin therapy is continued in order to maintain euglycemia while the islets engraft with the host tissue. It is important to avoid periods of hyperglycemia, as they increase the rate of beta cell apoptosis (Bruni et al. 2014). The period of neovascularization of islets occurs during the first 2–4 weeks posttransplant. After 2–3 months, insulin therapy is halted to assess graft function. For patients who do not achieve insulin independence after 3 months, a second infusion of donor islets may be necessary (Markmann et al. 2003).

Islet allotransplant recipients must follow an immunosuppression regimen to prevent rejection of the graft. Recent immunosuppression protocols have utilized T cell–directed antibodies. Two-drug pharmacotherapy is practiced for immunosuppression maintenance. A calcineurin inhibitor coupled with either a mammalian target of rapamycin inhibitor or mycophenolate mofetil is the most common maintenance regimen (Zsom et al. 2015). Immunosuppression in islet transplantation is a critical area that has evolved over time, with new options being investigated (Gangemi et al. 2008).

Evolution of and Advancements in Immunosuppressive Protocols

Early immunosuppressive protocols consisted of treatment with azathioprine, cyclosporine, and corticosteroids. Although azathioprine did not appear to have any adverse effects on islet function or insulin sensitivity, it is a relatively weak immunosuppressant. The introduction of cyclosporine, a potent immunosuppressive drug that blocks the clonal expansion of resting T cells, was revolutionary in whole-organ transplants (Calne et al. 1979). However, a 1984 study initially reported that cyclosporine exhibited diabetogenic potential in patients. Further studies revealed harmful effects on mouse islets (Andersson et al. 1984), rat islets (Robertson 1986), and human islets (Nielsen et al. 1986) when exposed to cyclosporine in vitro. Corticosteroids are also potent immunosuppressive drugs and act on the entire immune system. Like cyclosporine, corticosteroids carry diabetogenic side effects for patients and suppress the entire immune system. Avoiding corticosteroid treatment is critical in the success of islet transplantation.

The Edmonton protocol established a less diabetogenic and corticosteroid-free regimen that utilizes a combination of sirolimus with low-dose tacrolimus as immunosuppression maintenance, with induction achieved using daclizumab, an anti–IL-2 monoclonal antibody (Shapiro et al. 2000). Sirolimus works by blocking T and B lymphocyte responses to cytokines that are involved in the recruitment, activation, and expansion of T and B cells. Tacrolimus shares many of the same intracytoplasmic pathways to inhibit calcineurin. However, tacrolimus is about 10–100 times more potent in vitro (Yoshimura et al. 1989). The concept of using sirolimus as an effective immunosuppression maintenance drug was introduced in canines (Yakimets et al. 1993; Shibata et al. 2001) and further validated in pigs (Shibata et al. 2001) before being introduced in humans.

Achieving a permanent state of recipient tolerance toward an islet allograft remains an

important goal. Some islet groups are hoping to eliminate the need for immunosuppression entirely. Cell encapsulation represents a novel method of blocking the recipient's immune system from destroying the graft by providing a membrane around the islets. The membrane surrounding the islets contains pores that are large enough to allow nutrients and insulin to be exchanged between host and graft but small enough to block immune cells from attacking the islets.

Changes to current immunosuppressive regimens represent another route of future improvements. Groups in Minnesota and Miami have experimented with anti–tumor necrosis factor alpha (TNF-α) drugs along with current immunosuppression drugs. It has been shown that TNF-α exhibits negative effects on islet function and engraftment (Farney et al. 1993). Etanercept and infliximab are TNF-α–inhibiting drugs that have been proposed. Ten consecutive islet transplants were performed at the University of Edmonton using infliximab in addition to the standard regimen, but no positive impact was found when compared with controls (Maffi et al. 2007).

Alemtuzumab is used extensively in whole-organ transplants as a monoclonal antibody to CD52. A study conducted at the University of Alberta tested the efficacy of alemtuzumab as an induction agent and compared it with the standard induction approach. Findings suggested that alemtuzumab improves engraftment and the insulin independence rate but requires high doses of concomitant tacrolimus and mycophenolate mofetil (Pepper et al. 2013).

The University of Minnesota is currently testing the effects of HuOKT3γ1, a humanized anti–CD3-specific antibody, as an induction agent with sirolimus and tacrolimus maintenance. Anti-CD3 treatment depletes effector T cells and drives remaining T cells to a Th2 response. The use of anti-CD3 has been reported to induce tolerance in nonautoimmune models of allograft transplant, as well as to slow the progression of recent-onset diabetes in humans.

Other potential future immunosuppressive options are being examined. Anti-thymoglobulin induction, blockade of immunoregulatory pathways, T-reg induction, and targeting of dendritic cells all represent plausible future directions in immunosuppression for allogeneic islet transplantation (Posselt et al. 2010; Turgeon et al. 2010).

Outcomes of Islet Transplantation

Transplanting allogeneic islets is a highly effective method of preventing severe hypoglycemia and dramatic fluctuations in blood glucose levels (Ryan et al. 2005). It is for this reason that the current critical indication for islet transplant is a history of hypoglycemic episodes resulting from hypoglycemia unawareness. Islet recipients are protected from hypoglycemia as long as there is graft function, regardless of exogenous insulin intake.

At well-established islet transplant institutions, most islet transplant recipients achieve insulin independence. At the three most experienced islet transplant centers in North America (University of Alberta, University of Miami, and University of Minnesota), 82% of recipients were insulin independent at 1 year posttransplant between 2000 and 2005 (Shapiro et al. 2000, 2005; Froud et al. 2005; Hering et al. 2005). Many early recipients reported a loss of insulin independence after the first year, which led researchers to make improvements to immunosuppression protocols. Refinements of immunosuppression have resulted in increased long-term insulin independence. Early recipients received IL-2 receptor antagonists alone for immunosuppression induction, while current patients receive T cell–depleting agents and TNF-α blockade. With the current immunosuppression protocols, half of all recipients maintain insulin independence for at least 5 years posttransplant (Barton et al. 2012; Bellin et al. 2012).

While many recipients receive islets from two to three donor pancreases, it is possible to achieve long-term insulin independence with islets from a single donor. In 2005, it was reported that eight out of eight patients receiving T cell–depleting immunosuppression achieved insulin independence after a single donor infusion (Hering et al. 2005).

Although transplant centers have focused on maintaining euglycemia and preventing hypoglycemia through islet transplants, recent findings suggest that islet transplants are also effective in halting complications attributed to diabetes. Over an 8-year period, the University of British Columbia compared the progression of early microvascular disease between islet transplant recipients and patients maintaining strict exogenous insulin therapy. Progression of retinopathy occurred in 12% of medically treated patients, while no islet transplant recipients experienced any progression. Additionally, islet recipients experienced less decline in glomerular filtration rate than medically treated patients, suggesting less diabetic nephropathy following islet transplantation (Markmann et al. 2003; Thompson et al. 2011a).

Current Challenges

Nonimmunologic Problems Related to Islet Isolation

Islet isolation is a time-consuming procedure that involves a digestion phase and a purification phase. The islets are separated from the exocrine tissue by the chemical activity of collagenases and neutral proteases that are infused in the pancreatic duct as solution and allowed to activate for complete cleavage of the extracellular matrix proteins of the pancreas. The digestion is usually carried out in a special digestion device that keeps the enzyme solution recirculating, while mechanical shaking ensures a gentle disruption of the tissue over time. Subsequently, the islets are separated from the exocrine tissue during a purification step that exploits the difference in density between acinar and endocrine cells (Lakey et al. 1999).

The procedure itself leads to some loss of islet mass, as the destructive activity of the enzymes may damage cells or an inefficient purification may result in loss of islets among the more dense exocrine tissue. Donor characteristics, such as age, cause of death, long ischemia, and medical status, are also known to affect the quality of the islets (Balamurugan et al. 2014c). Other studies have indicated that destruction of the extracellular matrix has a negative impact on islet survival. Recently, several factors associated with the isolation procedure have been shown to have a deleterious impact on islets. It was previously demonstrated that in human islets, the isolation processing triggers the activation of pathways such as nuclear factor kappa–light-chain-enhancer of activated B cells (NF-kB) and poly ADP ribose polymerase (PARP), leading to apoptosis of the beta cells(Bottino et al. 2004). Antioxidants and other maneuvers aimed at reducing cell damage appear to efficiently protect islets during isolation and improve survival rates when added to the culture (Bottino et al. 2002a). Besides islet cell loss, the effects of isolation stress appear to be relevant to islets once infused into the recipient.

New data have recently shown that islet function is already undermined by stressful events prior to transplantation (Paraskevas et al. 2000; Bottino et al. 2004). These findings point to the effects of organ procurement, cold storage time, and the isolation procedure itself as potential threats to islets. Nonphysiologic, biophysical, and biochemical ambient conditions that occur during organ procurement and isolation require abrupt metabolic adaptation by islets, which may result in functional impairment and eventually cell death. Despite efforts to optimize the conditions of pancreas preservation ex vivo (Hering et al. 2002; Tsujimura et al. 2002) and the islet isolation process as a means to improve islet yield, only a limited part of the islet pancreatic content survives the process of isolation and subsequent culture.

Although the cascade of events occurring during isolation of pancreatic cells, which may cause cell dysfunction and ultimately death, is not fully characterized, new lines of research have indicated in rodents (Blinman et al. 2000; Pileggi et al. 2001) as well as humans (Bottino et al. 2002a) that oxidative stress plays a major role in triggering death of the islets and of the surrounding exocrine tissue. Other reports have demonstrated that oxidative stress is strongly connected to the adverse effects of chronic hyperglycemia on insulin biosynthesis by islet cells (Evans et al. 2003; Hoeldtke et al. 2003;

Robertson et al. 2003; Hoeldtke et al. 2011). It has been widely reported that islet cells are highly susceptible to oxidative stress because of their reduced levels of endogenous antioxidants (Azevedo-Martins et al. 2003). Under extreme conditions of stress, the islet antioxidant defenses may become overwhelmed, leading to a state of redox imbalance and production of reactive oxygen species (ROS).

One potential ROS-dependent target molecule is NF-αB. It is now known that NF-αB is a key transcription factor involved in regulating proinflammatory cytokines, chemokines, adhesion molecules, and inflammatory enzymes. Blockage of NF-αB – by administration of an NF-αB decoy or by using antisense oligonucleotide treatment – protects α cells from the effect of IL-1-α–induced nitric oxide production (Giannoukakis et al. 2000; Quan et al. 2001). Furthermore, it has recently been demonstrated that the native enzyme manganese superoxide dismutase delivered to mouse islets by gene therapy approaches is beneficial in improving islet cell survival after transplantation (Bertera et al. 2003).

Obstacles in Islet Allotransplant

A number of factors currently limit the widespread practice of pancreatic islet allotransplantation to treat T1DM. The largest obstacle is the shortage of human donor pancreases. Many donated pancreases are not suitable for islet transplantation due to previous medical/social history. Even if donor pancreases are available and suitable for islet isolation and transplantation, it is difficult to consistently obtain a high yield of viable islets due to variabilities between donors. When pancreases from young donors are available, the islets that are released during the isolation procedure are often heavily embedded (Balamurugan et al. 2006). Embedded islets make it difficult to purify islets during separation process, which results in many lost islets.

The current isolation protocol calls for the infusion of islets into the portal vein. The infusion process triggers an inflammatory reaction termed instant blood-mediated inflammatory response (IBMIR) (Cabric et al. 2007; Naziruddin et al. 2014). This reaction causes massive cell loss due to coagulation cascades that result in clot formation and leukocyte infiltration of the islets, leading to disruption of islet integrity and destruction of islets. Additionally, the liver is not an ideal site for cell infusion. The low oxygen supply and exposure to toxins from the gastrointestinal tract are cause for concern for long-term graft survival.

Immunosuppression regimens represent another barrier in the field of islet transplant. The toxicity of currently available immunosuppressive drugs presents a heavy burden on the patient and on the transplanted islets. The side effects associated with immunosuppressive drugs include, but are not limited to, mouth sores, upset stomach, diarrhea, increased cholesterol levels, decreased kidney function, and increased susceptibility to infection (Van Belle and von Herrath 2008).

Finally, islet allotransplantation is not internationally recognized as a clinical therapeutic procedure. As the isolation procedure is very time consuming and expensive, it is difficult to find sustainable funding for continued transplants. In Canada, islet allotransplants are considered a clinical therapeutic procedure so that active islet transplant facilities can be reimbursed for providing the treatment. In the USA, however, islet transplantation is considered experimental. However, CIT Consortium data will be submitted to the FDA to obtain biological licensure. Successful licensure will inevitably recognize islet transplantation as a clinical therapy, which will expand the therapeutic benefit for patients with T1DM in the USA.

Alternative Cell Sources for Islet Transplantation...

Islet transplantation has been shown to be a viable treatment option for patients afflicted with T1DM. However, the shortage of available human pancreases is a major obstacle for it to become a widespread treatment option. To establish islet

transplantation as a treatment for all T1DM patients, alternative cell sources will be required. Currently, two options are being explored as potential alternative cell sources: pig islets and human stem cells.

Pig Islets

The use of pig islets for xenotransplantation has been extensively studied as an alternative cell source. The rationale for porcine islets stems from the historical use of porcine insulin to treat T1DM, prior to the use of biosynthesized recombinant insulin. Additionally, glucose physiology is similar in pigs and humans, indicating functional compatibility. The ability to ramp up breeding of pigs specifically for this purpose would create a large and readily available source of islets (Zhu et al. 2014). To prevent rejection of pig islets, encapsulation devices have been used to protect against the human immune response generated by porcine cell surface antigens. Encapsulation of cells is performed by placing cells in a semipermeable hydrogel that allows the passing of nutrients and oxygen between the encapsulated cells and the host but blocks immune regulators from attacking the transplanted tissue. Encapsulation can also provide protection from xenosis, which has been a concern in the use of animal cells in humans. However, transplantation of pig islets may represent a nearly insurmountable immunological barrier in humans.

In 2006, two independent groups reported the first long-term graft survival (>6 months) of pig islets in nonhuman primates and provided the realistic potential for clinical islet xenotransplantation (Cardona et al. 2006; Hering et al. 2006). Since then, several other groups have reported long-term pig islet graft survival in diabetic nonhuman primates. Very recently, Shin et al. (2015) reported consistent long-term islet survival by transplanting adult pig islets in five consecutive rhesus monkeys, with the longest survival being >603 days following transplantation. Other groups have also demonstrated the positive results of using genetically engineered source pigs for islet xenotransplantation. When compared with wild-type pig islet recipients, alpha 1, 3-galactosyl transferase-gene knockout (GTKO) pig islets (Thompson et al. 2011b) and hCD46 transgenic pig islets (van der Windt et al. 2009) have shown better graft survival. Others have also observed variable survival gains by using multiple genetically engineered pigs in both cynomolgus monkeys (Bottino et al. 2014) and baboons (Hawthorne et al. 2014).

In 1994, Groth et al. attempted the first clinical xenotransplantation by transplanting fetal porcine islet-like cell clusters (ICC) into ten insulin-dependent diabetic kidney transplant patients (Groth et al. 1994). The ICCs were transplanted intraportally or under the kidney capsule. Four patients excreted small amounts of porcine C-peptide in urine for 200–400 days. In one renal graft biopsy specimen, morphologically intact epithelial cells stained positive for insulin and glucagon in the subcapsular space (Groth et al. 1994).

In a Mexican study (Valdes-Gonzalez et al. 2005), pig islets were cotransplanted with Sertoli cells in a stainless steel chamber that was implanted under the skin of patients. No immunosuppressive drugs were administrated at any point during the study. Half of the patients had a significantly reduced insulin requirement compared with both their pretransplant levels and with controls, and this reduction was maintained for up to 4 years. Two patients became insulin independent for several months. Porcine insulin was detected in three patients' sera following glucose stimulation up to 4 years posttransplant. Three years posttransplant, one of four devices was removed from four patients, and the presence of insulin-positive cells in the transplant was demonstrated by immunohistology in all four patients (Valdes-Gonzalez et al. 2005).

A study performed in China by Wang et al. involved transplanting neonatal pig islets into the hepatic artery of 25 T1DM patients treated with relevant immunosuppression (Wang et al. 2011). Again, the clinical benefits to these patients were negligible. In a clinical study performed in New Zealand (Elliott et al. 2007), pig islets were encapsulated in alginate and transplanted into the intraperitoneal cavity of

patients as an immunoisolating approach to avoid the need for immunosuppression therapy. By 12 weeks posttransplant, one patient's insulin dose was significantly reduced by 30% ($P = 0.0001$ by multiple regression tests) from 53 units daily prior to transplant. The insulin dose returned to pretransplant level at week 49. Improvement in glycemic control continued as reflected by total glycated hemoglobin of 7.8% at 14 months from a pretransplant level of 9.3%. Urinary porcine C-peptide peaked at 4 months (9.5 ng/mL) and remained detectable for 11 months (0.6 ng/mL). The patient was followed as part of a long-term microbiologic monitoring program, which showed no evidence of porcine viral or retroviral infection. At laparoscopy 9.5 years after transplantation, abundant nodules were seen throughout the peritoneum. Biopsies of the nodules showed pacified capsules containing cell clusters that stained as live cells under fluorescence microscopy. Immunohistology noted sparse insulin and moderate glucagon staining cells. The retrieved capsules produced a small amount of insulin when placed in high glucose concentrations in vitro. An oral glucose tolerance test induced a small rise in the serum of immunoreactive insulin, identified as porcine by reversed-phase high-pressure liquid chromatography (Elliott et al. 2007).

However, safety concerns in using xenografts need to be considered. One major concern is the potential for zoonosis (Brown et al. 1998; Patience et al. 1998; Mullon 1999; Platt 2000), which applies not only to the recipient but also to the population at large. Even with regulations to develop designated pathogen-free pig sources (Cooper and Casu 2009; Hering et al. 2009; Schuurman 2009), long-term follow-up of patients receiving xenografts will be required to identify potentially yet unidentified pathogens (Schuurman 2015). One reason for this is that humans have preformed anti-Gal antibodies; Gal (galactose-α1,3-galactose) is an oligosaccharide expressed in pig endothelium (Zeyland et al. 2013). As a result, there is immediate complement activation as anti-Gal antibodies bind to the surface of the transplanted pig islets. In addition, xenografts activate a more robust instant blood-mediated inflammatory reaction (Kourtzelis et al. 2015). Following transplantation, platelets cause macroscopic coagulation of the islets, leading to the recruitment of complement components as a secondary response. The resulting inflammatory response contributes to large islet losses. Together, these issues mean that patients would have to be placed on intensive immunosuppressive regimens for pig islet survival – which is less than ideal due to the morbidity of immunosuppression agents.

Human Stem Cells

In vitro, different cell types can be differentiated into functioning beta cells that respond to glucose stimulation by secreting insulin. Beta cells generated from such cell sources could be transplanted for patients suffering from T1DM, which makes these cells a potential alternative source to exogenous insulin treatment.

Embryonic stem cells. Research studies have demonstrated that embryonic stem cells can be differentiated into insulin-producing cells (Assady et al. 2001; Shi 2010; Hua et al. 2014). Such differentiated insulin-producing cells can be cryopreserved until needed, easily expanded, and differentiated in vitro. The advantage of these cells is the unlimited capacity for self-renewal. However, there are major limitations; besides ethical considerations, patients need immunosuppression to prevent rejection, as these cells would be foreign to the recipients' immune system. The side effects of high blood glucose levels would be replaced by the side effects of immunosuppression and, moreover, cells would be rejected after some time, even with immunosuppression. Due to these potential drawbacks as well as ethical considerations, these cells seem, in fact, to be suboptimal candidates for future beta cell replacement therapies (Bavister et al. 2005).

Induced pluripotent stem cells. The limitations of embryonic stem cells, including the ethical considerations, can be overcome using induced pluripotent stem cells, even though these cells can be generated from somatic cells and share properties with embryonic stem cells.

Moreover, induced pluripotent stem cells would be available for the future recipient, and there is no need for immunosuppression after transplantation. In 2010, Alipio et al. (2010) demonstrated the reversal of hyperglycemic conditions in an in vivo diabetic animal model using these cells. After reprogramming skin fibroblasts to become induced pluripotent stem cells, cells were differentiated using an established protocol for embryonic stem cell differentiation. The generated cells produced insulin in response to glucose stimulation in vitro, and in a mouse model of type 2 diabetes, transplantation of these cells ameliorated hyperglycemia. In another model, blood glucose levels were normalized after cell transplantation in mice with streptozotocin-induced diabetes.

Mesenchymal stem cells. Mesenchymal stem cells can easily be extracted from various tissues (e.g., bone marrow and adipose tissue, among other sources) and depending on cytokines and cell–cell interactions can differentiate into various cell types that form bone, cartilage, adipose tissue, and hepatocytes. In 2011, Phadnis et al. demonstrated that human bone marrow–derived mesenchymal stem cells can differentiate into endocrine pancreatic cells (Phadnis et al. 2009). In vivo, secretion of human C-peptide was present after transplantation of these cells into pancreatectomized and streptozotocin-induced diabetic mice; using transplantation of human bone marrow–derived mesenchymal stem cells, normoglycemia could be maintained. In recent clinical trials, the potential of these cells in treating type 1 and type 2 diabetes was demonstrated. Vanikar et al. isolated mesenchymal stem cells from adipose tissue, differentiated them into insulin-producing cells, and performed cotransplantation with cultured bone marrow cells in patients with T1DM (Trivedi et al. 2008). Hemoglobin A1c levels decreased, less insulin was needed, and C-peptide serum levels increased in these patients. In another clinical trial in type 2 diabetic patients, transplantation of placenta-derived mesenchymal stem cells led to increased C-peptide levels as well as a decreased need for insulin (Jiang et al. 2011). The easy availability of mesenchymal stem cells, the successful early clinical trials, and the promising in vitro and in vivo experiments render these cells a promising candidate for transplantation-based therapies to overcome diabetes.

Liver cells. Studies have demonstrated that liver cells can also be used to generate beta cells. Yang et al. showed that cultures of mouse embryo liver cells generated insulin-positive cells when transduced with an adenoviral vector encoding three genes: *Pdx1, Ngn3,* and *MafA* (Yang et al. 2013). In another study, Sapir et al. demonstrated that PDX-1-treated human liver cells expressed insulin, stored it in defined granules, and secreted the hormone in a glucose-regulated manner (Sapir et al. 2005). When these cells were transplanted under the renal capsule of diabetic immunodeficient mice, the mice became normoglycemic for prolonged periods of time.

Pancreatic acinar cells, alpha cells, and duct cells. Studies have shown that it is possible to generate beta cells from adult human pancreatic cells. Recent work demonstrated that differentiated cell types in adult organs, including the mouse pancreas, can be experimentally "reprogrammed" into progeny resembling islet cells, suggesting a new strategy for beta cell replacement (Vierbuchen and Wernig 2011). For example, adult mouse pancreatic acinar cells can be converted into insulin-producing cells in vitro and in vivo (Minami et al. 2005; Zhou et al. 2008). The islet alpha cell is another closely related cell type that has been studied for reprogramming into insulin-producing cells. Recently Thorel et al. (2010) demonstrated by lineage tracing in a mouse model of beta cell ablation that a large fraction of regenerated beta cells originated from alpha cells.

Pancreatic ducts constitute 30–40% of the human pancreas and have been proposed as a potential source of replacement beta cells (Bouwens and Pipeleers 1998; Bonner-Weir et al. 2004). During pancreas development, fetal endocrine cells derive from primitive ductal epithelium (Bonner-Weir et al. 1993; Pan and Wright 2011). In addition, some studies have suggested that in adult mice, beta cells may be produced from pancreatic ductal epithelium (Rovira et al. 2010). In humans, prior studies have suggested that adult human primary ductal cells

in heterogeneous cell mixtures may harbor the potential to generate endocrine-like progeny (Swales et al. 2012), but interpretation in these studies was limited by the probability of islet cell contamination. Therefore, the potential for conversion of pancreatic ductal cells toward an endocrine fate remains unclear. Moreover, prior studies have revealed only a limited proliferative capacity of primary human pancreatic ductal cells in culture (Rescan et al. 2005). Thus, despite their relative abundance, multiple practical issues have prevented development of human pancreatic ductal cells as a source of replacement beta cells.

Conclusion

Since its introduction in 1974, the practice of clinical islet transplantation has made enormous strides, to the point that more than two-thirds of recipients are free from insulin at 1 year and more than half at 5 years. In these selected patients with difficult-to-control diabetes, islet transplantation has been shown to restore euglycemia, prevent severe hypoglycemia, and reduce microvascular complications. Progress has been made in islet isolation procedures and in immunosuppression. Nevertheless, the procedure is limited by being considered experimental in the USA as well as by a shortage of available human pancreases. Stem cells – and in particular mesenchymal stem cells – may be able to overcome this shortage, while progress continues in other areas of islet preparation and infusion.

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Cross-References

▶ Autologous Islet Cell Transplant
▶ Donor Evaluation and Procurement
▶ Infectious Issues After Pancreas Transplant

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Pathology of Pancreas Transplant

Cinthia B. Drachenberg and John C. Papadimitriou

Contents

Abstract

Accurate determination of the cause of pancreas allograft dysfunction requires histological evaluation of the transplanted organ. Guidelines are available for systematic morphological evaluation and optimal clinicopathological integrations. Furthermore, morphological characterization of the main histopathological types of acute rejection, T-cell-mediated rejection (TCMR) and antibody mediated allograft rejection (AMR), has allowed for a better differentiation from each other and from other non-rejection-related pathological processes.

Acute TCMR is characterized by active parenchymal cellular infiltrates composed predominantly of T cells and typically involving veins, ducts, acini, and occasionally arterial branches. The main differential diagnosis of

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TCMR includes infectious processes such as cytomegalovirus infection and EBV-related posttransplant lymphoproliferative disorder, both of which also present with inflammatory cellular infiltrates.

Significant parenchymal involvement in acute AMR, on the other hand, is characterized by predominantly macrophagic (± neutrophilic) inflammation and typically C4d-positive microvasculature injury. Patchy or diffuse hemorrhagic necrosis in AMR requires consideration of a different set of differential diagnoses, mainly including ischemic pancreatitis and vascular graft thrombosis due to technical issues.

Accurate diagnosis of TCMR and AMR, as well as mixed forms of rejection, requires (1) systematic analysis of the histological features, (2) evaluation of C4d staining, and (3) determination of the DSA status.

Keywords

Pancreas allograft biopsy · Pancreas transplantation · T-cell-mediated rejection · Antibody-mediated rejection · C4d · Donor-specific antibodies · Interacinar capillaries · Chronic rejection · Graft sclerosis · Banff grading schema · CMV pancreatitis · PTLD

Introduction

The clinical diagnosis of acute pancreas allograft rejection relies heavily on laboratory methods indicating abnormalities in the exocrine products (i.e., amylase, lipase) and/or the endocrine function (e.g., blood glucose control). Exocrine drainage into the urinary bladder allows for serial measurements of amylasuria which if decreased >25% or >50% from the baseline are most consistent with acute allograft rejection (Prieto et al. 1986, 1987; Nankivell et al. 1990; Sollinger et al. 1998; Gruessner 2004). On the other hand, decrease in urine amylase is not specific and can be seen also in acute pancreatitis, graft thrombosis, and duct obstruction. Decrease in urinary amylase had a specificity of only 30% and a positive predictive value of 53% when compared with biopsy diagnosis of rejection (Moukarzel et al. 1992; Benedetti et al. 1995).

Increase in amylase and lipase in serum is a marker of acinar cell injury and is useful for monitoring pancreas patients, independent of the exocrine drainage technique (Prieto et al. 1986, 1987; Nankivell et al. 1990; Allen et al. 1991b; Moukarzel et al. 1992; Papadimitriou et al. 1998). Similar to measurements in urine, serum amylase and lipase lack specificity because these parameters also increase in acute pancreatitis and other inflammatory processes involving both the native and the transplanted pancreas. In acute rejection, the level of the pancreatic enzymes correlates well with the lower rejection grades, and very pronounced increase in serum amylase and lipase more often correlates with severe rejection, although there is significant variability from patient to patient (Papadimitriou et al. 1998).

Endocrine abnormalities such as hyperglycemia are relatively rare, occurring more often in severe or irreversible acute rejection typically associated with extensive parenchymal necrosis (Drachenberg et al. 1997; Papadimitriou et al. 1998). In addition to severe rejection, hyperglycemia can be caused by other processes (i.e., recurrence of autoimmune disease, islet cell drug toxicity, and chronic rejection) (Sutherland et al. 1989; Burke 2011).

Due to the nonspecific nature of the laboratory tests (Klassen et al. 1996), *needle core biopsies* are considered the gold standard for diagnosis of rejection (Allen et al. 1991a, 1991b; Kuhr et al. 1995; Bartlett et al. 1996a, b; Boonstra et al. 1997; Laftavi et al. 1998a, b; Papadimitriou et al. 1998; Lee et al. 2000; Papadimitriou 2002; Atwell et al. 2004; Casey et al. 2005).

Needle core biopsies are usually done under ultrasound or computer tomographic guidance, with 18- or 20-gauge needles (Klassen et al. 1995, 2002; Aideyan et al. 1996). Adequate tissue can be obtained in 88–90% of instances (Bernardino et al. 1990; Gaber et al. 1992, 2001; Kuhr et al. 1995; Aideyan et al. 1996; Klassen et al. 1996, 2002; Lee et al. 2000). Significant complications have been reported in 2–3% of cases (Aideyan et al. 1996; Klassen et al. 2002). Laparoscopic biopsies or open surgical wedge biopsies are used if the pancreas is not accessible percutaneously (Silver et al. 1997; Laftavi et al. 1998b, Kayler et al. 2002). The latter

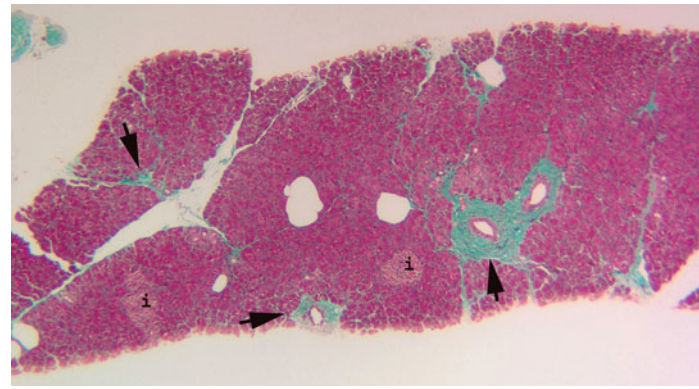

Fig. 1 Example of needle core biopsy of pancreas allograft stained with trichrome stain for identification of collagen in septal areas (*arrows*). Note the lack of collagen in lobular areas. Normal islets are also present (i)

technique has been recommended if a diagnosis of recurrence of autoimmune type 1 DM is suspected, in order to allow for the examination of a larger number of endocrine islets (Vendrame et al. 2010; Burke et al. 2011; Pugliese et al. 2011).

In patients with bladder drainage, *cystoscopic transduodenal pancreas biopsies* can provide clinically useful information in the same manner as percutaneous core biopsies, but adequate pancreatic tissue is only obtained in 57–80% of cases (Carpenter et al. 1990; Perkins et al. 1990; Casanova et al. 1993; Jones et al. 1994; Lowell et al. 1994; Nakhleh et al. 1995a, b). More recently it has been proposed that duodenal samples obtained through upper gastrointestinal endoscopy from enteric drained pancreas allografts anastomosed to the proximal jejunum can be used to monitor the grafted pancreas. With this technique (*enteroscopic duodenal cuff biopsies*), Margreiter et al. (2012) obtained diagnostic material in 75% of cases and identified pathological changes in a third of them. When the procedure was performed in patients with pancreas dysfunction, the duodenal sample demonstrated features consistent with rejection in 65% of cases (Margreiter et al. 2012). A similar approach has been used by others (Zibari et al. 2014).

Determination of Pancreas Transplant Biopsy Adequacy

Although the adequacy of any particular biopsy sample is ultimately determined by the examining pathologist, it is generally recommended that pancreas graft biopsies contain at least three lobular areas and their associated interlobular septa (Fig. 1). The latter typically contain veins and branches of the pancreatic duct. Arterial branches that follow separate courses, irregularly embedded in the parenchyma, are sampled with more difficulty. Due to the diagnostic importance ascribed to the arterial lesions, it is recommended that the absence of arterial branches be specifically stated in the pathology report (Drachenberg et al. 2008).

Practical Guidelines for Processing Pancreas Allograft Biopsies

For best diagnostic yield, it is recommended that at least two hematoxylin- and eosin-stained sections are examined from two different levels of the core. Five to ten adjacent/intervening unstained sections should be available in order to perform additional stains as needed (i.e., CMV stain).

It is recommended that C4d immunostain is performed in all biopsies (Melcher et al. 2006; Carbajal et al. 2007; Drachenberg et al. 2011).

Masson's trichrome stain can aid in the identification of specific structures or pathological changes (e.g., arterial walls, fibrinoid necrosis) and is also indicated in biopsies with suspected chronic rejection to demonstrate incipient interacinar fibrosis (Papadimitriou et al. 2003; Drachenberg et al. 2008).

In patients biopsied due to hyperglycemia, it is essential to perform stains for insulin and

glucagon to identify selective loss of beta cells indicating recurrence of autoimmune disease (Tyden et al. 1996; Burke 2011).

Congo red stain should be performed to identify islet amyloid deposition, if any amount of eosinophilic extracellular material is identified within the endocrine islets (Leon Fradejas et al. 2015).

Relationship Between Pancreas and Kidney Rejection

Although acute rejection in kidney and pancreas grafts often occur together (synchronously) (Severyn et al. 1982; Vogt et al. 1992; Nakhleh et al. 1993; Gruessner et al. 1994), the histological grade or severity of rejection may be discordant between the two organs (Gruessner et al. 1994, 1997).

In practice, it is assumed that SPK transplants either reject synchronously, or at least sequentially, with kidney rejection occurring earlier than pancreas rejection (Severyn et al. 1982; Hawthorne et al. 1997). On the other hand, it is important to remember that asynchronous rejection has been amply documented in SPK recipients (Reinholt et al. 1988, Bartlett et al. 1996a,b). In a large study, based on concurrent biopsies of both organs, the pancreas and kidney were selectively involved by rejection in 22% and 13% of instances, respectively. The possibility of isolated rejection underscores the need for performing selective renal or pancreatic biopsy evaluation even in patients with SPK (Bartlett et al. 1996a,b, Klassen et al. 1996).

A more recent study with concurrent analysis of pancreas and renal allograft biopsies also demonstrated a high degree of discordance between the two organs (38%), highlighting the importance of organ-specific tissue monitoring (Troxell et al. 2010).

Banff Schema for Diagnosis and Grading of Allograft Rejection

The Banff schema puts emphasis on the categorical differentiation of the features of cell-mediated and antibody mediated allograft rejection (AMR), since they are subject to different therapeutic approaches (Troxell et al. 2010; Drachenberg et al. 2008).

The schema also contemplates other pathological findings identified in pancreas biopsies including islet pathology and the development of chronic rejection/graft sclerosis. The latter typically leads to progressive impairment of glucose homeostasis and is usually accompanied by a gradual decrease in the levels of amylase and lipase in urine and/or serum (Drachenberg et al. 2001; Humar et al. 2003).

Timely diagnosis of rejection in pancreas transplants is of paramount importance to prevent subsequent development of graft sclerosis (Munivenkatappa et al. 2012; Kandaswamy et al. 2013). Repeated episodes of acute rejection, and particularly late acute rejection, significantly increase the risk for graft loss due to chronic rejection (Basadonna et al. 1993; Tesi et al. 1994; Stratta 1998a, b, c; Drachenberg et al. 2001; Stegall 2001; Papadimitriou 2006).

Banff Schema: Diagnostic Categories General Considerations

The diagnosis and grading of rejection are based on the global assessment of the biopsy.

The pancreas Banff schema includes eight diagnostic categories that cover the range of histopathological changes in pancreas allografts. Similar to other transplanted organs, the two main forms of allograft rejection are recognized and characterized morphologically: T-cell-mediated rejection (TCMR) and antibody mediated allograft rejection (AMR) (Matsukuma et al. 1998). For each of these rejection types, acute and chronic histological manifestations are identified and severity grades are defined (Drachenberg et al. 2008, Drachenberg et al. 2011).

Specific Histological Features Utilized for the Diagnosis of Rejection

– *Septal inflammatory infiltrates*, predominantly mononuclear, including (activated) lymphocytes and variable numbers of eosinophils (Fig. 2).

- *Venulitis*, defined as subendothelial accumulation of inflammatory cells and endothelial damage observed in septal veins (Fig. 3).
- *Ductitis*, defined as epithelial infiltration of branches of the pancreatic ducts by mononuclear or eosinophilic inflammation and evidence of ductal epithelial cell damage (Fig. 2).
- *Neural and perineural inflammation* of intrinsic parenchymal nerve branches.
- *Acinar inflammation*, defined by the presence of inflammatory infiltrates with similar characteristics as the septal infiltrates amidst the exocrine acini (Fig. 4).
- *Single-cell and confluent acinar cell necrosis/apoptosis* in association to the acinar inflammation.
- *Intimal arteritis*, defined as infiltration by mononuclear cells under the arterial endothelium (Fig. 5).
- *Necrotizing arteritis*, defined as transmural inflammation with focal or circumferential fibrinoid necrosis (Fig. 6).
- *Interacinar accumulation of neutrophils and/or macrophages* with or without capillary dilatation (capillaritis) (Fig. 7a–d).
- *Microvascular injury* characterized by congestion of interacinar capillaries with small or

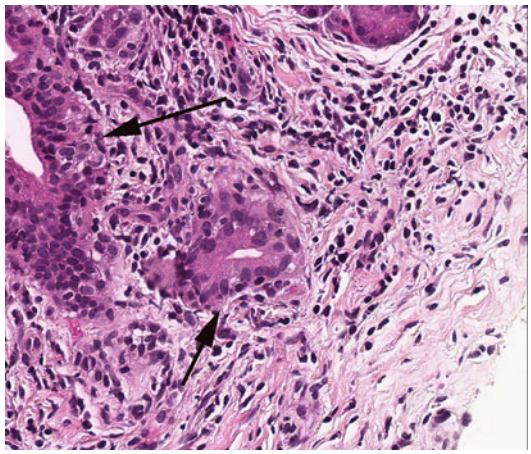

Fig. 2 Inflammatory septal infiltrates. Ducts are permeated by the inflammatory cells (ductitis, *arrows*)

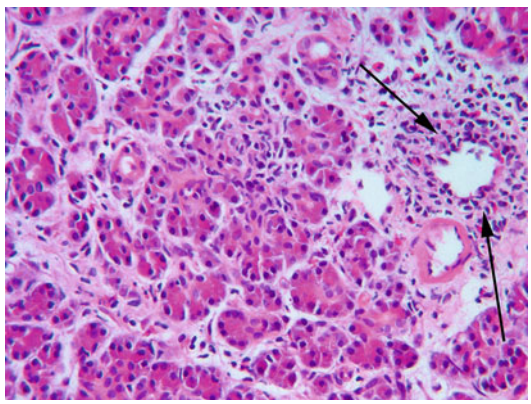

Fig. 3 Mild inflammatory infiltrates within pancreatic acini and venous inflammation (venulitis, *arrows*)

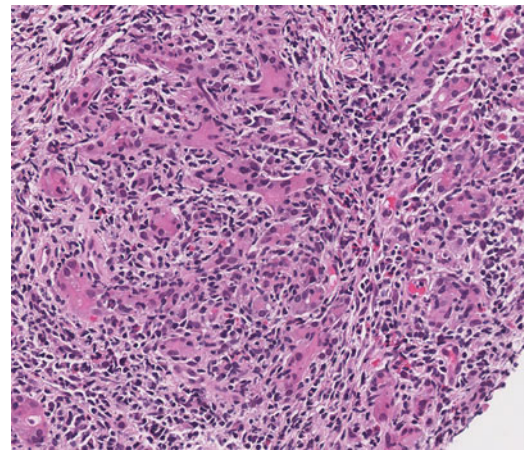

Fig. 4 Acute T-cell-mediated rejection with severe inflammation of exocrine pancreas tissue with reactive degenerative changes in the acini which appear with irregular contours and nuclear atypia

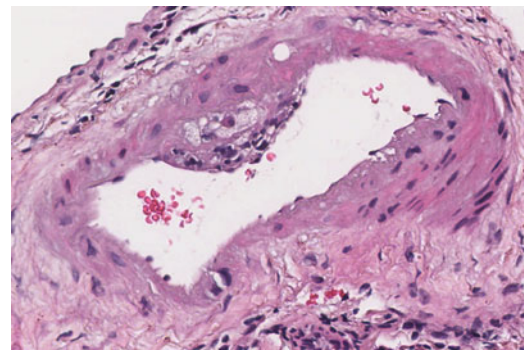

Fig. 5 Acute rejection with arterial inflammation (intimal arteritis). Lymphocytic inflammation of the intima leads to lifting of the endothelium. The muscular layer is viable

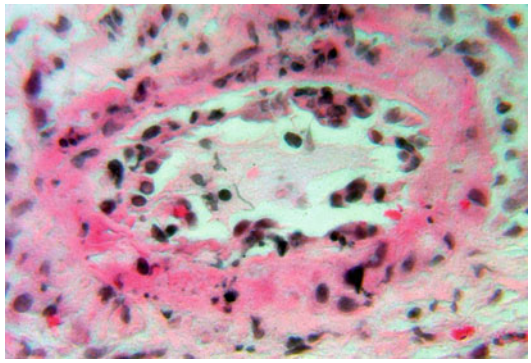

Fig. 6 Severe acute rejection with necrotizing arteritis. In addition to intimal arteritis, there is fibrinoid necrosis of the arterial wall appearing with loss of the cellular detail of the muscular layer and bright-red discoloration

confluent microhemorrhages that may be associated with foci of tissue necrosis. Microvascular thrombi.

– *C4d-positive staining in interacinar capillaries* (IAC) as a feature of antibody-mediated rejection, if in association with donor-specific antibodies in serum.

Grading of Acute Allograft Rejection

Determination of the severity of acute T-cell-mediated rejection is based on the evaluation of several components as described in Table 1. Specifically, *inflammation confined to the septa and septal structures* (veins, ducts) represents milder forms of rejection, more responsive to antirejection treatment and less likely to result in irreversible sclerosing sequelae (Papadimitriou 2006). In contrast, *intimal arteritis and necrotizing arteritis* define the more severe forms of acute pancreas rejection, because these arterial lesions are more refractory to antirejection treatment and are known to carry an increased risk for immediate and subsequent graft thrombosis/loss and transplant arteriopathy (Drachenberg et al. 2001). The *extent of acinar inflammation* (focal vs. multifocal diffuse) and the *presence and extent of acinar cell injury* are also used to determine rejection severity based on evidence that extensive acinar injury and damage can lead to fibrosis and accelerated graft loss, if untreated or undertreated (Papadimitriou 2006).

Diagnostic Categories: Main Differential Diagnoses

Banff Category 1: Normal

Normal-appearing biopsies with no inflammation or fibrosis are more often encountered in protocol biopsies of well-functioning grafts (Drachenberg et al. 1997, 2004).

A "normal"-appearing biopsy in a patient biopsied for graft dysfunction can be seen in the following situations:

1. Late phase of recurrent autoimmune disease, i.e., after resolution of isletitis (Sibley et al. 1985; Sutherland et al. 1989; Burke 2011). This process can only be recognized by the evaluation of immunohistochemical stains for insulin and glucagon to demonstrate selective loss of beta cells.
2. Drug toxicity that is primarily characterized by vacuolization and damage of islet cells (Drachenberg et al. 1999).
3. Very mild (grade 1) acute antibody-mediated rejection may appear with an essentially normal biopsy as described in the first well-documented case (Melcher et al. 2006). C4d staining and performance of donor-specific antibody studies are essential to rule out antibody-mediated rejection in these cases.
4. Very early, mild T-cell-mediated rejection can be missed in the biopsy due to sampling error.

Banff Category 2: Indeterminate for Rejection

Inactive-appearing focal septal inflammation which does not fulfill the criteria for mild rejection (i.e., partial cuffing of a septal vein or ducts) but lacking any evidence of endothelial of epithelial involvement.

Similar to the "borderline" category in the kidney, the differential diagnosis of a biopsy with these features includes early or treated acute rejection. Alternatively the findings may represent nonspecific chronic inflammation (Drachenberg et al. 1997, 2004; Papadimitriou et al. 1998).

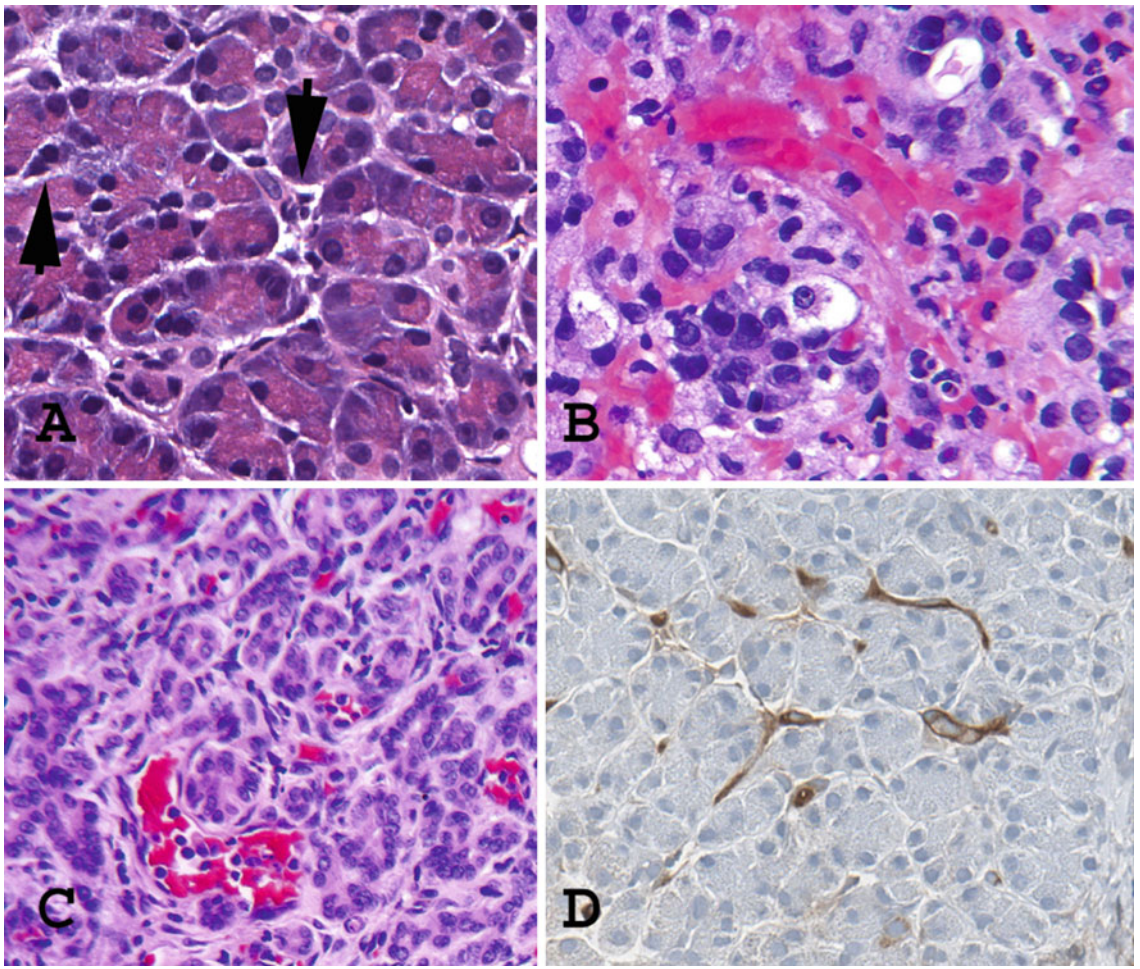

Fig. 7 Acute antibody-mediated allograft rejection (AMR). (**a**) Very subtle mononuclear inflammation in interacinar capillaries (*arrows*). (**b**) More pronounced changes in acute AMR leading to dilatation of interacinar capillaries and damage of acinar cells (vacuolization, dropout). (**c**) Capillaritis defined as congested interacinar capillaries containing mononuclear cells. (**d**) C4d-positive stain in interacinar capillaries

Table 1 Banff pancreas allograft rejection grading schema – 2011 update

Diagnostic categories[a]
1. Normal. Absent inflammation **or** inactive septal, mononuclear inflammation not involving ducts, veins, arteries, or acini. There is no graft sclerosis. The fibrous component is limited to normal septa and its amount is proportional to the size of the enclosed structures (ducts and vessels). The acinar parenchyma shows no signs of atrophy or injury
2. Indeterminate. Septal inflammation that appears active but the overall features do not fulfill the criteria for mild cell-mediated acute rejection
3. Acute T-cell-mediated rejection
Grade I/mild acute T-cell-mediated rejection Active septal inflammation (activated, blastic lymphocytes, ± eosinophils) involving septal structures: venulitis (subendothelial accumulation of inflammatory cells and endothelial damage in septal veins) and ductitis (epithelial inflammation and damage of ducts) **and/or** Focal acinar inflammation. No more than two inflammatory foci[b] per lobule with absent or minimal acinar cell injury
Grade II/moderate acute T-cell-mediated rejection (requires differentiation from AMR) Multifocal (but not confluent or diffuse) acinar inflammation (≥3 foci[b] per lobule) with spotty (individual) acinar cell injury and dropout **and/or** Mild intimal arteritis (with minimal, <25% luminal compromise)
Grade III/severe acute T-cell-mediated rejection (requires differentiation from AMR) Diffuse (widespread, extensive) acinar inflammation with focal or diffuse multicellular/confluent acinar cell necrosis **and/or** Moderate or severe intimal arteritis, >25% luminal compromise **and/or** Transmural inflammation – necrotizing arteritis
4. Antibody-mediated rejection (AMR, see diagnostic components below*) *Confirmed circulating donor-specific antibody (DSA) *Morphological evidence of tissue injury (interacinar inflammation/capillaritis, acinar cell damage swelling/necrosis/apoptosis/dropout, vasculitis, thrombosis) *C4d positivity in interacinar capillaries (IAC, ≥5% of acinar lobular surface) **Acute AMR** 3 of 3 diagnostic components* **Consistent with acute AMR** 2 of 3 diagnostic components* **Requires exclusion of AMR** 1 of 3 diagnostic components* See separate table for histological grading of acute AMR[b] **Chronic active antibody-mediated rejection** – combined features of categories 4* and 6 in the absence of features of category 3
5. Chronic allograft arteriopathy. Arterial intimal fibrosis with mononuclear cell infiltration in fibrosis
6. Chronic allograft rejection/graft fibrosis
Stage I (mild graft fibrosis) Expansion of fibrous septa; the fibrosis occupies less than 30% of the core surface, but the acinar lobules have eroded, irregular contours. The central lobular areas are normal
Stage II (moderate graft fibrosis) The fibrosis occupies 30–60% of the core surface. The exocrine atrophy affects the majority of the lobules in their periphery (irregular contours) and in their central areas (thin fibrous strands crisscross between individual acini)
Stage III (severe graft fibrosis) The fibrotic areas predominate and occupy more than 60% of the core surface with only isolated areas of residual acinar tissue and/or islets present
7. Islet pathology Recurrence of autoimmune DM Insulitis Selective ß-cell loss Islet amyloid (amylin) deposition Islet cell drug toxicity
8. Other histological diagnoses. Pathological changes not considered to be due to acute and/or chronic rejection. For example, CMV pancreatitis, PTLD, etc.

Adapted from Drachenberg and Papadimitriou (2004)

Notes:

[a]Categories 2–8 may be diagnosed concurrently and should be listed in the diagnosis in the order of their clinicopathological significance

[b]Histological grading of acute AMR described in main text

In an earlier study, only half of the patients with biopsies showing *indeterminate* features responded to antirejection treatment (Papadimitriou et al. 1998).

Banff Category 3: Acute T-Cell-Mediated Rejection

Acute TCMR is graded as mild, moderate, or severe (grades I, II, and II, respectively), based on the identification of lesions that are associated with progressively worse outcomes (Nakhleh and Sutherland 1992; Boonstra et al. 1997; Drachenberg et al. 1997; Papadimitriou et al. 1998; Papadimitriou 2006). Specifically evaluated is the presence of septal and acinar inflammation, as well as inflammatory involvement of ducts, veins, and arteries.

T-cell-mediated rejection requires the following differential diagnoses considerations:

1. Due to the potentially focal nature of early rejection, very mild forms of rejection are liable to sampling variation errors. Clinically significant rejection, however, can be typically identified in an adequate needle pancreas biopsy (Drachenberg et al. 1997).
2. CMV pancreatitis, which is often patchy in nature and requires high degree of suspicion with low threshold for the performance of CMV immunostains (Klassen et al. 2000).
3. Identification of extensive cellular inflammatory infiltrates in the pancreas parenchyma requires differentiation from EBV-related posttransplant lymphoproliferative disorder (PTLD). The latter include benign-appearing hyperplastic lymphoplasmacytic proliferations as well as overtly malignant lymphoid proliferations (lymphoma). Evaluation of T- and B-lymphocyte markers and EBV studies are necessary for the diagnosis of PTLD.
4. Severe T-cell-mediated rejection with parenchymal or vascular necrosis requires the exclusion of a component of acute antibody-mediated allograft rejection. Evaluation of C4d stains and correlation with donor-specific antibody studies are part of the essential workup in these cases.

Banff Category 4: Antibody-Mediated Rejection

Antibody-mediated rejection (AMR) presents with a wide range of morphological changes ranging from subtle microvascular inflammation to confluent hemorrhagic parenchymal necrosis (Melcher et al. 2006; Carbajal et al. 2007; Papadimitriou 2007; Torrealba et al. 2008; de Kort et al. 2010, 2013; Rangel et al. 2010, Troxell et al. 2010). AMR is caused by antibodies directed against donor-specific human leukocyte antigen (HLA) molecules or other cell surface antigens (Einecke et al. 2009) and more often results from a strong anamnestic antibody response to previous antigenic exposure. Posttransplant development of de novo donor-specific antibody (DSA) may also occur, similar to other solid organ transplants (Gaber 2007; Einecke et al. 2009; Fabio et al. 2010; Waki et al. 2010; Zanone et al. 2010; Katerinis et al. 2011; Loupy et al. 2011).

The diagnosis of *acute pancreatic AMR* is based on the clinicopathological combination of (**a**) circulating donor-specific antibodies, (**b**) morphological evidence of microvascular tissue injury (see below), and (**c**) C4d staining in interacinar capillaries. A diagnosis of "suspicious for AMR" is reached if only two of the three elements are present, but the identification of only one diagnostic element is not sufficiently diagnostic or "suspicious" of AMR. Graft dysfunction is not required for the diagnosis of acute AMR (Drachenberg et al. 2011).

The differential diagnosis of acute AMR varies with the severity of the process as follows:

1. Early AMR can be very subtle, presenting only with some lobular inflammation, with these findings erroneously being considered "nondiagnostic" unless the biopsy is evaluated with a high degree of suspicion and accompanied by C4d staining and correlation with DSA status (Drachenberg et al. 2011).

Biopsies with minimal or absent inflammation, particularly in patients with hyperglycemia, also require differentiation from other pathological processes such as recurrence of autoimmune diabetes (Burke et al. 2011) or other islet-related abnormalities (Drachenberg et al. 2011). For an accurate assessment of the state of the endocrine islets, it is essential to perform insulin and glucagon immunostains. This is particularly important in patients biopsied for hyperglycemia, where the quantitative relationship of beta/alpha cells needs to be evaluated in order to address specific cell-type loss (i.e., beta cell loss in recurrence of type 1 DM) (Burke et al. 2011).

2. Extensive hemorrhagic necrosis in severe AMR may resemble early thrombosis related to "technical failure." Critical evaluation of the samples is necessary for distinction of these two entities (Drachenberg et al. 2001; Muthusamy et al. 2010).

Diagnosis and treatment of AMR require serological studies for circulating DSA at regular intervals after transplantation, at the time of biopsy, and whenever rejection is suspected. From the histological point of view, evaluation of C4d stains is essential for the diagnosis of AMR. In pancreas allograft biopsies, C4d staining is typically absent in cases of pure acute pure acute TCMR or in protocol biopsies from well-functioning grafts (Torrealba et al. 2008; de Kort et al. 2010).

Both immunohistochemical and immunofluorescence C4d stains are adequate for diagnosis and yield a similar staining pattern in interacinar capillaries (IAC).

Grading of Acute AMR

The severity of AMR is graded histologically as mild, moderate, or severe according to the extent of the interacinar infiltrates and the extent of microvascular injury and tissue damage as follows:

Grade I/mild acute AMR: well-preserved architecture, mild monocytic-macrophagic or mixed (monocytic-macrophagic/neutrophilic) infiltrates with rare acinar cell damage, and minimal or no evidence of microvascular injury.

Grade II/moderate acute AMR: overall preservation of the architecture with significant interacinar monocytic-macrophagic or mixed (monocytic-macrophagic/neutrophilic) infiltrates with or without evidence of capillary dilatation (capillaritis) *associated with* significant microvascular injury manifested as congestion and extravasation of red blood cells (microhemorrhages) and multicellular acinar cell injury and dropout.

Grade III/severe acute AMR: architectural disarray, scattered inflammatory infiltrates in a background of pronounced microvascular injury with interstitial hemorrhage, and multifocal and confluent parenchymal necrosis. Arterial and venous wall necrosis and thrombosis may be present (Drachenberg et al. 2011).

Chronic Active AMR

Chronic graft sclerosis/fibrosis with graft failure in association with persistent exposure to DSA leads to the characterization of this clinicopathological entity (Carbajal et al. 2007). The diagnosis of *chronic active AMR* requires the following elements: (a) morphological features of acute AMR (2 or 3 AMR diagnostic components, see Table 1), (b) the absence of features of ACMR, and (c) underlying graft fibrosis (Banff diagnostic category 6). In other words, this diagnosis indicates that graft fibrosis or graft loss is attributed primarily to ongoing AMR. C4d stain positivity is typically identified in residual lobules (Drachenberg et al. 2011). Fibrinoid necrosis in vascular walls and thrombosis (recent or organized) are findings supportive of ongoing antibody-mediated rejection. Correlation with the presence of donor-specific antibodies is required for this diagnosis (Melcher et al. 2006; Carbajal et al. 2007; Papadimitriou 2007; Solez et al. 2007).

Mixed ACMR and AMR

This pathological entity is characterized by C4d positivity with documented DSA in combination

with features of T-cell-mediated rejection (see Table 1) (de Kort et al. 2010). If combined features are present, it is important that the pathology report clearly indicates the type of rejection present (AMR, ACMR, or mixed), estimates the degree of activity (mild, moderate, or severe) of each process, and indicates the extent of fibrosis (stage) (Drachenberg et al. 2011).

Banff Category 5: Chronic Allograft Arteriopathy

This category is defined by the presence of "active transplant arteriopathy" characterized by narrowing of the arterial lumen by a subendothelial proliferation of fibroblasts, myofibroblasts, and smooth muscle cells with superimposed evidence of ongoing inflammatory activity. The latter consists of infiltration of the subintimal fibrous proliferation by mononuclear cells, typically T cells and macrophages (Fig. 8).

Chronic allograft arteriopathy increases the risk of late graft thrombosis and graft loss (Drachenberg et al. 2001).

Arterial lesions may be present in both, TCMR and AMR (Hirohashi, Lefaucher, Sis, Solez).

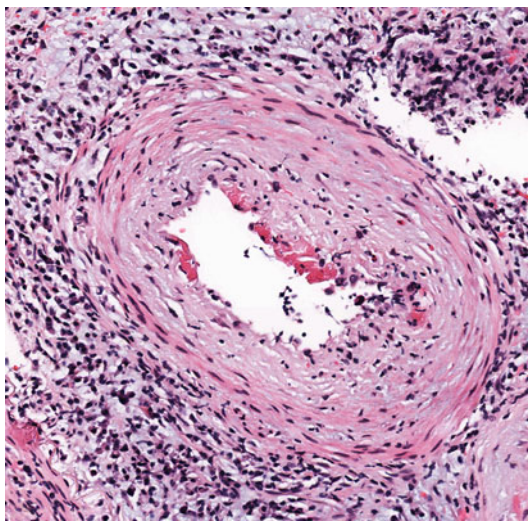

Fig. 8 Active transplant arteriopathy. The arterial wall is fibrotic due to subendothelial proliferation of fibroblasts, myofibroblasts, and smooth muscle cells with superimposed evidence of ongoing inflammatory activity

Banff Category 6: Chronic Allograft Rejection/Graft Sclerosis

Histological grading of chronic rejection/graft sclerosis in the pancreas has been shown to correlate with graft survival, i.e., mild fibrosis is associated with lengthy graft survival, and severe fibrosis heralds a limited time of remaining graft function (Papadimitriou et al. 2003). Furthermore, despite its notoriously patchy nature, the progression of pancreas allograft fibrosis can be reliably assessed in core biopsies through the established semiquantitative grading schema that is both simple and reproducible. Grading is based on the semiquantitative determination of the proportion of sclerotic/fibrotic areas versus the remaining acinar/lobular tissue (Papadimitriou et al. 2003).

Three grades are recognized in this diagnostic category, mild graft sclerosis (chronic grade I), moderate graft sclerosis (chronic grade II), and severe graft sclerosis (chronic grade III), based on the identification of <30, 30–60, and $>60\%$ of fibrosis in the biopsy core, respectively (Fig. 9).

Banff Category 7: Islet Pathology

Preservation of islet integrity and function is the main objective of pancreas transplantation. Unfortunately a significant proportion of patients require insulin administration despite receiving a technically successful pancreas transplant (Waki 2010).

The main purpose of this category is the recognition of recurrent autoimmune diabetes mellitus (characterized by *insulitis* (*isletitis*) and/or *selective ß-cell loss*) and deposition of *islet amyloid* (amylin) and islet cell *drug toxicity* (Leon Fradejas et al. 2015; Westermark 2011; Burke 2011; Drachenberg 1999 and Vendrame et al. 2010). Table 2 describes the main morphological changes in this category.

Banff Category 8: Other Histological Diagnosis

A variety of other pathological processes affecting the pancreas allografts have histopathological manifestations. Identification of any of these

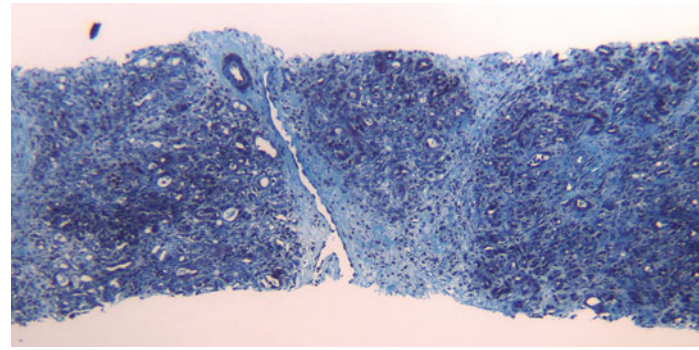

Fig. 9 Chronic rejection/graft sclerosis. Trichrome stain highlights expanded fibrotic septa and corresponding atrophy of the acinar tissue. Compare with n which shows normal pancreas parenchyma

Table 2 Islet pathology in pancreas allografts: morphological features[a]

Diagnosis	Hematoxylin and eosin histological finding	Special studies
Recurrence of autoimmune (type 1 DM)	Early stages: islet inflammation *insulitis* (*or isletitis*), lymphocytic infiltrates localize to the islets with no involvement of other areas of the parenchyma Advanced stages: autoimmune attack of insulin-producing cells leads to s*elective loss of β-cells*. The overall islet architecture usually remains within normal limits Early and late stages occur sequentially in individual islets but are not temporally uniform throughout the pancreatic parenchyma leading to potential sampling errors The exocrine parenchyma is typically preserved and lacks inflammation. Nesidioblastosis may be present	In earlier stages T-cell stains highlight isletitis (islet inflammation); a mixed population of α- and β-cells is present in the inflammatory stage Insulin stain for β-cells and glucagon stain for α-Cells demonstrate selective loss of insulin-producing cells (only glucagon-producing cells persist in damaged islets. Isletitis subsides in cells with no residual β-cells
Islet cell calcineurin Inhibitor drug toxicity	In a background of architecturally preserved, non-inflamed, exocrine parenchyma, there is cytoplasmic swelling and vacuolization of islet cells. The islets appear optically clear and stand out from the more eosinophilic acinar parenchyma. Severe cases show islet cell dropout with formation of empty spaces (lacunae) and intra-islet apoptotic cell fragments	Insulin and glucagon stains demonstrate a mixed population of α- and β-cells Electron microscopy demonstrates predominant damage to β-cells
Islet amyloidosis (Development of type 2 DM)	Focal or diffuse extracellular accumulation of pale eosinophilic material in the endocrine islets only. Large amount of islet amyloid leads to disarray of islet morphology as the amyloid replaces islet cells Islet amyloid is a characteristic of type 2 DM and results from fibrillary aggregation of islet amyloid polypeptide (IAPP), a hormone normally co-secreted with insulin	Congo red stain is necessary to confirm the presence of amyloid within the islets Insulin and glucagon stain demonstrate a mixed population of α- and β-cells
Nesidioblastosis	Identification of insulin-producing cells in pancreatic ductal epithelium. These changes likely represent aberrant differentiation and are most likely regenerative in nature	Insulin stain is necessary to identify endocrine differentiation of epithelial cells

[a]Based on references (Leon Fradejas et al. 2015; Vendrame et al. 2010)

Table 3 Non-rejection-related inflammation in pancreas transplants

Diagnosis main histological findings	
Posttransplant ischemic pancreatitis	Cell type: neutrophils, foamy macrophages Location: mostly septal Other features: fat necrosis, edema, and interstitial hemorrhage. Patchy coagulation necrosis of clusters of acinar cells may be present. No fibrosis, the septa are expanded due to edema/fat necrosis
Peripancreatitis/peripancreatic fluid collection	Cell type: mixed (lymphocytes, plasma cells, eosinophils, neutrophils) Location: septa and periphery of lobules Other features: dissecting bundles of active fibroblastic proliferation with obliteration of septal structures, relative preservation of lobules (cirrhotic appearance)
Cytomegalovirus pancreatitis	Cell type: mostly lymphocytes Location: septal and acinar, patchy Other features: cytomegalovirus cytopathic changes in acinar, endothelial, and stromal cells. Fibrosis may be present if there is underlying chronic rejection CMV stain should be evaluated.
Posttransplant lymphoproliferative disorder	Cell type: variable, polymorphic with lymphoblasts, plasma cells, eosinophils in low-grade disease to monomorphic, predominantly lymphoid in high-grade disease (lymphoma) Other features: lymphoid proliferation is nodular, expansive. Necrosis may be present EBV, T and B cell stains should be evaluated.
Bacterial or fungal infection	Cell type: varies. Purulent inflammation, abscesses, and granulomas Location: random Other features: same as bacterial and fungal infections in other organs

processes may be achieved in isolation or concurrently with other diagnostic categories in the pathology schema (Drachenberg et al. 1998; Klassen et al. 2000; Drachenberg and Papadimitriou 2004; Paraskevas et al. 2005).

Main non-rejection pathological processes identified in pancreas biopsies are listed in Table 3.

Cross-References

- ▶ Follow-Up Care of the Pancreas Transplant Recipient
- ▶ Infectious Issues After Pancreas Transplant
- ▶ Surgical Complications of Pancreas Transplant

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Medical Evaluation of the Diabetic Patient for Pancreas Transplant

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Contents

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Abstract

Pancreas transplantation has the ability to restore normoglycemia in patients with insulin-dependent diabetes mellitus. As a result, it can potentially improve the quality of life and reduce the deleterious effects of the secondary complications of diabetes mellitus. Pancreas transplant surgery has a significant risk of surgical and infectious complications, although these risks are decreasing as more experience in the field is gained. A long-term mortality benefit for pancreas transplantation has not been shown and the selection of the potential pancreas transplant candidate must be strict. Risk factors for pancreas transplantation include older age, cardiovascular disease, and peripheral vascular disease. There are three different options for pancreas transplantation: (1) pancreas transplantation alone, (2) pancreas after kidney transplantation, and (3) simultaneous pancreas and kidney transplantation. Pancreas transplant alone is reserved for the patient who has adequate kidney function. The decision to perform pancreas after kidney transplantation or simultaneous pancreas and kidney transplantation should be made on an individual basis. Both options are superior to deceased donor kidney transplantation alone but do not appear to have a survival benefit compared to living donor kidney transplantation alone.

Keywords

Pancreas · Transplant · Diabetes · Hypoglycemia · Kidney · Indications

Introduction

The prevalence of diabetes mellitus in the USA has more than tripled over the past two decades. In 2012, 29.1 million Americans carried the diagnosis of diabetes mellitus, including 1.25 million with insulin-dependent diabetes mellitus (IDDM). The incidence of diabetes mellitus in the USA was 1.7 million diagnoses per year. Diabetes mellitus was the 7th leading cause of death in the USA in 2010 (ADA 2014). The secondary complications of diabetes mellitus result in increased mortality and significantly impact the quality of life of the diabetic patient.

Diabetic nephropathy is the leading cause of end-stage renal disease in the USA and was responsible for 44% of all new cases in 2011 (ADA 2014). The incidence of coronary artery disease is increased resulting in higher rates of cardiovascular mortality. Peripheral neuropathy results in gastroparesis, erectile dysfunction, urine retention, and autonomic dysfunction with associated debilitating orthostatic hypotension and increased risk of sudden cardiac death. Peripheral vascular disease results in an increased rate of strokes and amputation. Hypoglycemic unawareness is a dangerous complication that often limits the vocational ability and independence of the diabetic patient.

Pancreas transplantation provides insulin and, as a result, has the potential to cure IDDM which is characterized by insulin deficiency. The merits of pancreas transplantation for non-insulin dependent diabetes mellitus (NIDDM) are controversial and will be discussed later in this chapter. Successful pancreas transplantation does not necessarily improve the secondary complications of diabetes mellitus but, in most instances, may help retard the progression of these complications.

Due to the presence of significant comorbidities, the medical transplant evaluation of the diabetic patient is very complex. The potential benefits of pancreas transplantation (improvement in secondary complications, improved quality of life, and improved patient survival) must be weighed against the significant risks of pancreas transplant surgery and immunosuppressive medications. As part of the process of predicting which patients will experience these benefits, it is important to understand the effects pancreas transplantation has on secondary diabetic complications and mortality. It is also important to identify and address the various risk factors in the potential pancreas transplant recipient so that they can be addressed pretransplant. In addition, identification of these risk factors may help the transplant physician exclude certain patients from receiving a

pancreas transplant due to excessive risk. Finally, it is important to determine which option of pancreas transplantation is optimal for the patient who also needs a kidney transplant.

Secondary Diabetic Complications and the Effects of Pancreas Transplantation

Peripheral Neuropathy

Peripheral neuropathy is the most common secondary complication of diabetes mellitus. Although estimates vary, it is generally felt that the prevalence of some type of peripheral neuropathy in diabetic patients is over 50% (Boulton et al. 2005). Peripheral neuropathy is often classified into two broad categories: (a) chronic sensorimotor distal symmetric polyneuropathy (DPN) and (b) diabetic autonomic neuropathy.

DPN results in reduced distal limb sensation, thus increasing the risk of diabetic foot ulcers and amputation. In addition, DPN can cause painful neuropathy and significantly impact the diabetic patient's quality of life. Diabetic autonomic neuropathy results in several clinical manifestations, including cardiac autonomic neuropathy (resting tachycardia, poor exercise tolerance, orthostatic hypotension, and increased risk of sudden death), gastrointestinal disturbances (gastroparesis and constipation), impotence, and neurogenic bladder.

Several studies have evaluated the effects of pancreas transplantation on peripheral neuropathy. One study compared 115 patients who underwent pancreas transplantation versus a control group of diabetic patients (Navarro et al. 1997). The study found that the clinical symptoms attributed to peripheral neuropathy improved. In addition, sensory and motor testing, nerve conductions studies, and autonomic function tests also improved. Another study measured heart rate variability (HRV) in 30 patients pre- and post-pancreas transplantation (Cashion et al. 1999). HRV is a marker of cardiac autonomic dysfunction and diminished values are associated with an increased risk of sudden cardiac death (Algra et al. 1993). The study found that 12-month HRV is significantly improved in pancreas transplant recipients, although not to the level of healthy control subjects.

The effect of pancreas transplantation on gastroparesis was evaluated in 42 simultaneous kidney-pancreas (SPK) recipients. The authors found that gastric motility studies normalized in some subjects while others shifted from bradygastria to tachygastria post-transplant. The use of prokinetic and antisecretory medications was increased after transplantation (Cashion et al. 2004). It is possible that the gastrointestinal side effects of immunosuppressive medications were a confounding factor and made interpretation of the data from this study difficult.

A study of 10 SPK patients demonstrated improved sexual function in comparison to IDDM patients who did not undergo pancreas transplantation (Salonia et al. 2011). This same study did not demonstrate similar improvements in patients who received a pancreas transplant alone (PTA). Another study in SPK recipients showed that 41% of patients self-reported improvement in sexual function after transplantation, 51% did not note any change, and 7% felt they had worse sexual function (Jürgensen et al. 2008).

In general, it is believed that successful pancreas transplantation, as manifested by improved glycemic control, can potentially improve both DPN and diabetic autonomic neuropathy. Improvement in peripheral neuropathy may take several years to occur. However, complete reversal of peripheral neuropathy is unlikely to occur.

Retinopathy

Diabetic retinopathy is the most common eye disease in diabetic patients and can result in blindness. The prevalence of diabetic retinopathy in the USA in 2010 was 5.4% and differs slightly based on race, with the highest prevalence in the Hispanic population (8%). Approximately, one in three patients with diabetes mellitus has diabetic retinopathy (ADA 2014).

An early study done in 1988 did not note any improvement in diabetic retinopathy in 22 patients with IDDM who underwent successful pancreas transplantation at 24 months post-transplant (Ramsay et al. 1988). However, most subsequent studies seem to demonstrate improvement in diabetic retinopathy after pancreas transplantation. A study done in 48 SPK patients, with a median follow-up of 17 months, demonstrated stabilization and/or improvement in diabetic retinopathy in a majority of the subjects (Giannarelli et al. 2005). The same group demonstrated improvement in diabetic retinopathy in 33 patients who received a PTA compared to a control group of 35 patients with IDDM (Giannarelli et al. 2006).

In summary, pancreas transplantation does appear to stabilize and potentially improve diabetic retinopathy. This underscores the importance of meticulous eye care in the diabetic patient pre-pancreas transplantation.

Coronary Heart Disease/Peripheral Vascular Disease

In 2010, the risk of a heart attack was 1.8 times greater and the risk of cardiovascular death was 1.7 times higher in adult diabetic versus nondiabetic patients in the USA. The risk of a stroke was 1.5 times higher in the adult diabetic patient and approximately 73,000 lower limb amputations took place in diabetic patients in 2010. The risk of coronary heart disease continues to increase in diabetic patients in the USA. In 2011, over 7 million patients with diabetes mellitus had a self-reported history of coronary heart disease and/or stroke (ADA 2014).

Cardiovascular events are the leading cause of death after pancreas transplantation. In a large single center cohort of 1,000 SPK's, cardiopulmonary events and stroke were responsible for 41.2% of deaths (Sollinger et al. 2009). However, studies have demonstrated reduced cardiovascular death and incidence of strokes, improved left ventricular function, and reduced peripheral vascular disease with pancreas and kidney transplantation compared to receiving a kidney transplant alone (La Rocca et al. 2001).

Demographics of the Different Types of Pancreas Transplantation

Pancreas Transplant Alone

Pancreas transplant alone (PTA) refers to transplantation of a pancreas allograft without previous or concurrent kidney transplantation. PTA is the least commonly performed type of pancreas transplant over the past decade and accounted for 13.5% of pancreas transplants in the USA in 2013. A total of 423 patients were listed for a PTA in the USA at the end of 2013 (Kandaswamy et al. 2015).

Pancreas After Kidney Transplant

Pancreas after kidney transplant (PAK) refers to transplantation of a pancreas allograft after previous kidney transplantation (different donor for each allograft). The rate of PAK has diminished over the past decade and accounted for 8.9% of pancreas transplants in the USA in 2013. A total of 533 patients were listed for a PAK in the USA at the end of 2013 (Kandaswamy et al. 2015).

Simultaneous Pancreas and Kidney Transplant

Simultaneous pancreas and kidney transplant refers to the simultaneous transplantation of the pancreas and kidney allograft from the same donor. SPK is the most common type of pancreas transplant and accounted for 77.6% of pancreas transplants in the USA in 2013. A total of 1,976 patients were listed for a SPK in the USA at the end of 2013 (Kandaswamy et al. 2015).

Pancreas Transplant Alone (PTA)

PTA is unique among pancreas transplantation in that previous or simultaneous kidney transplantation did/does not occur. As a result, the potential benefits of pancreas transplantation need to be measured against the risks of pancreas transplant surgery and the side effects of the immunosuppressive medications.

Benefits

The most commonly cited reason for PTA is recurrent hypoglycemia and hypoglycemic unawareness in the brittle diabetic patient. Hypoglycemic unawareness refers to the inability of the diabetic patient to sense when serum glucose levels are dangerously low. The Diabetes Control and Complications research group has previously shown that approximately 36% of all hypoglycemic episodes occurred without warning in awake patients (AM J Med 1991). The consequences of severe hypoglycemia can be devastating including seizures, coma, and death. Hypoglycemic unawareness significantly impacts quality of life, as patients are often times unable to work certain professions, operate heavy machinery, or drive. Another under-recognized consequence of hypoglycemic unawareness is the inability to strictly manage glucose levels with intensified insulin therapy due to the increased risk of hypoglycemia. Intensified insulin therapy has been shown to slow the progression of retinopathy and neuropathy and reduce microalbuminuria and albuminuria in type I diabetic patients (NEJM 1993). Even with standard insulin therapy, the chance of a severe hypoglycemic attack is 6–7 times higher in individuals with hypoglycemic unawareness compared to those without (Gold et al. 1994).

Another potential benefit of PTA is to reduce the progression of the secondary complications of diabetes mellitus. As noted previously in this chapter, successful pancreas transplantation potentially has a significant impact on diabetic peripheral neuropathy, autonomic dysfunction, retinopathy, and cardiovascular risk although most of the studies have been performed in SPK and PAK patients.

In addition, PTA can theoretically reduce the risk of diabetic nephropathy. A comparison of 32 IDDM patients who underwent PTA with 30 nontransplanted IDDM patients demonstrated that glycemic control was significantly improved which resulted in reduction of both micro- and macroalbuminuria (Coppelli et al. 2005). In a large retrospective data registry analysis, outcomes after PTA were followed from 1966–2011 in the USA (Gruessner and Gruessner 2013). The outcomes were further analyzed by separating the patients into recent eras. Only 6% of patients who underwent a PTA from 2002 to 2006 needed a kidney transplant at 5 years which is significantly improved compared to 21% of patients who underwent a PTA from 1994 to 1997. These data must be interpreted somewhat cautiously, however, as there was no true control group and a higher percentage of patients had a pretransplant calculated glomerular filtration rate of >70 ml/min in 2002–2006 compared to 1994–1997. In addition, the selection criteria for PTA likely differed significantly among individual transplant centers and among the different eras.

Risks

An important risk factor that has deterred transplant programs from routinely performing PTA is an increased risk of infection. Despite advances in the field of immunosuppression and an increasing number of medications available, suppression of the immune system still carries significant infectious morbidity and mortality risks.

Pancreas transplant recipients are at particular risk for infectious complications due to the numerous risk factors of diabetes mellitus, including incomplete bladder emptying, poor peripheral circulation, and impaired wound healing. The surgical implantation of the pancreas allograft is also associated with a high risk of infection due to the need for donor duodenum (a source of bacteria) to be attached to a nonsterile recipient organ. Enteric drainage of pancreas allograft function increases the risk of peritonitis while bladder drainage increases the risk of urinary tract infections. Despite advances in surgical technique, pancreas transplantation has historically resulted in the highest risk of infection compared to other solid organ transplants (Ozaki et al. 1992).

Opportunistic infections refer to infections that usually do not occur in the immunocompetent host. Patients who undergo PTA are at risk for these infections which include cytomegalovirus, *Pneumocystis jirovecii*, toxoplasmosis, Nocardia, and disseminated fungal infections. These infections are often difficult to diagnose and carry the risk of significant morbidity and mortality. The clinical severity of "common" infections, such as

urinary tract infection and community-acquired pneumonia, is increased in the setting of immunosuppression.

Another deterring factor for PTA is the increased risk of malignancy due to the immunosuppressive medications. Certain malignancies are felt to be viral mediated and the relative risk of infection-related malignancies in solid organ transplant recipients from the USA is 2.1 compared to the general population (Engels et al. 2011). In particular, the risk of non-Hodgkin's lymphoma in solid organ transplant recipients is more than sevenfold the risk in the general population. The relative risk of non-viral-mediated malignancies is also 2.1 compared to the general population. In particular, the risk of non-melanoma skin cancer in solid organ transplant recipients is approximately 14-fold the risk in the general population.

Implantation of the pancreas allograft is associated with significant surgical risk. Enteric drainage of pancreatic exocrine function has largely replaced bladder drainage. An early analysis of surgical complications in 112 enteric-drained SPK recipients demonstrated an 8% risk on enzymatic leak (Sollinger et al. 1998). Enzymatic leak results in peritonitis and urgent surgical reexploration is usually indicated. The same study demonstrated a 2.6% risk of intra-abdominal abscess and 12% risk of wound infection or dehiscence in 500 bladder- and enteric-drained SPK recipients. Fortunately, due to improved surgical technique, the risk of complications after implantation of the pancreas allograft has continued to decrease (Gruessner and Gruessner 2013).

PTA Versus Nontransplanted IDDM Patient

PTA does offer the potential to eliminate the debilitating effects of hypoglycemic unawareness and reduce the progression of secondary diabetic complications, including diabetic nephropathy, compared to nontransplanted IDDM patients. Studies have yet to demonstrate, however, that PTA is advantageous compared to the nontransplanted IDDM patient who has excellent glycemic control and no difficulties with hypoglycemic unawareness. Due to the significant risks of PTA, the selection process for PTA candidates needs to be stringent. Only individuals with frequent and unpredictable hypoglycemic episodes and/or "brittle" diabetes despite maximization of conventional diabetic therapy are likely to benefit from PTA. In addition, the PTA candidate should have adequate kidney function (minimum glomerular filtration rate of 40 ml/min).

It is important for potential PTA candidates to understand that there are no long-term data demonstrating improved survival after PTA versus remaining on conventional therapy. In fact, an analysis of PTA recipients in the USA from 1995 to 2000 demonstrated a relative risk of mortality in the first 4 years post-transplant of 1.57 for PTA recipients versus those who remained on conventional therapy (Venstrom et al. 2003). Of note, the relative risk approached statistical significance and the 4-year patient survival for PTA recipients was 85.2%. However, a more recent registry analysis demonstrated a 5-year patient survival for PTA recipients of over 90% (Gruessner and Gruessner 2013). It is likely that PTA is becoming a safer procedure and, as a result, older PTA survival and complication analyses need to be evaluated cautiously.

Certain recipient risk factors have been associated with increased risk of patient and graft loss after PTA and include cardiovascular disease and peripheral vascular disease, as these are the two most common etiologies for patient mortality after PTA (Kandaswamy et al. 2015). As a result, the patient with established cardiovascular disease (previous history of myocardial infarction, ischemic cardiomyopathy, multiple cardiac stents, coronary bypass surgery) or peripheral vascular disease (claudication, amputation, extensive tobacco use, lower extremity bypass surgery, carotid artery disease, history of transient ischemic attack/stroke) may not be a suitable PTA candidate. The pretransplant evaluation of the PTA candidate should, at minimum, include pharmacologic stress testing of the heart and evaluation of peripheral circulation by an experienced transplant and vascular surgeon. The need for routine cardiac catheterization has not been established in solid organ transplantation and

should be utilized at the discretion of the individual transplant center. An abnormal stress test, however, should prompt cardiac catheterization.

PTA Versus Islet Cell Transplantation

In patients who are deemed suitable candidates for PTA, it is important to realize that islet cell transplantation is another option for achieving normoglycemia. Islet cell transplantation may be a suitable option for patients who are deemed high surgical risk candidates as the procedure is much simpler compared to pancreas transplantation. Historically, the rate of insulin independence has been lower with islet cell transplantation compared to pancreas transplantation despite recent improvements in outcomes (Barton et al. 2012). However, more recent studies have reported insulin independence rates after islet cell transplantation that approach the historically reported rates in PTA (Bellin et al. 2012 and Shapiro et al. 2010). One of the main limiting factors for islet cell transplantation for IDDM patients in the USA is that it is considered experimental and investigational by insurance companies and the cost is often times prohibitive.

Pancreas After Kidney Transplant (PAK)

PAK is offered to diabetic patients who have previously undergone a successful kidney transplant. PAK differs from simultaneous pancreas and kidney transplantation (SPK) in two ways: (1) the pancreas and kidney allografts are from different donors in PAK and (2) the kidney allograft may be from a living or deceased donor in PAK whereas the kidney allograft is always from a deceased donor in SPK.

Similar to PTA, the benefits of PAK must be weighed against the risks of pancreas transplant surgery and increased exposure to immunosuppressive medications. In addition, the merits of PAK versus SPK will be discussed later in this chapter.

Benefits

The potential benefits of PAK are similar to PTA, including reducing the progression of the secondary complications of diabetes mellitus as outlined previously in this chapter. In theory, successful PAK can reduce the risk of diabetic nephropathy in the kidney allograft.

Risks

PAK versus deceased donor or living donor kidney transplant alone involves a second surgery. As outlined previously, pancreas transplant surgery entails significant surgical risk. A large analysis of PAK recipients demonstrated that the relative risk of mortality in the first 90 days after PAK is 5 compared to remaining on the wait-list for a transplant (Venstrom et al. 2003). In addition, a second round of intensified immunosuppression is needed which increases the risk of malignancies and infections. In particular, kidney transplant recipients are at risk of polyoma virus-associated nephropathy due to their immunocompromised state. Further exposure to a heavy immunosuppressive burden can further increase this risk. It is imperative that potential PAK recipients are screened for polyoma-virus prior to undergoing pancreas transplantation.

Another concern for PAK is increased exposure to calcineurin inhibitors. Calcineurin inhibitors are known to be nephrotoxic and their levels are intentionally run higher the first several weeks post-transplant. In theory, increased calcineurin inhibitor exposure can reduce long-term kidney allograft survival.

PAK Versus Kidney Transplantation Alone

Several studies have attempted to investigate the merits of PAK versus kidney transplant alone. One study followed 47 PAK recipients and demonstrated that the mean serum creatinine level at the time of pancreas transplant increased from 1.5 to 2.0 mg/dL 1 year post-transplant and the

iothalamate GFR decreased from 61 ± 22 mL/min pre-PAK to 43 ± 17 mL/min 1 year post-PAK (Larson et al. 2004). The data must be interpreted carefully, however, since all of the PAK recipients were bladder drained and the transplants took place from 1998 to 2002. The majority of PAKs are now enteric drained and the outcomes after pancreas transplantation have continued to improve (Gruessner and Gruessner 2013). In addition, 20% of the PAK patients had a deceased donor kidney transplant and patients were accepted for PAK regardless of pre-pancreas transplant renal allograft function. In the present day, the majority of PAK recipients have received a previous living donor kidney transplant and most transplant programs have a minimal level of renal allograft function that is required before being cleared for PAK listing. A more recent study analyzed 307 patients with IDDM who underwent living donor kidney transplantation (Kleinclauss et al. 2009). 175 of these patients subsequently underwent PAK and 75 patients met inclusion criteria to receive a PAK but did not receive a pancreas transplant. A comparison of these two groups showed similar patient and kidney allograft survival at 1, 5, and 10 years after kidney transplantation. Interestingly, long-term kidney allograft survival (>60 months) was significantly better in the PAK group if the pancreas transplant took place between 2 and 12 months after kidney transplantation. This data indicated that PAK does not negatively influence short- or long-term patient and kidney allograft survival and, in fact, may help improve long-term kidney allograft survival if done within 1 year of kidney transplantation. The reason for this latter finding is not entirely clear but early glycemic control after pancreas transplantation can theoretically prevent diabetic lesions from occurring in the kidney allograft. Interestingly, another study found that if the pancreas transplant is performed more than 3 years after kidney transplantation, there is an increased risk of kidney allograft loss (Luan et al. 2012). These studies suggest that early performance of PAK is important. In a multivariate analysis for patient mortality, the only significant risk factor was patient age ≥ 45 years old (relative risk of death of 1.99) (Kleinclauss et al. 2009). Most transplant programs do have an upper age limit for pancreas transplant eligibility. Similar to previous studies, the main cause of patient mortality was cardiovascular disease. This once again reinforces the importance of strict cardiac screening prior to pancreas transplantation.

Simultaneous Pancreas and Kidney Transplantation (SPK)

SPK is offered to IDDM patients who have Stage IV-V chronic kidney disease or end-stage renal disease. As opposed to PAK, both the pancreas and kidney allografts are from the same deceased donor and the both allografts are placed in the recipient during a single operation. The benefits of kidney transplantation and pancreas transplantation must be weighed against the risks of kidney and pancreas transplant surgery as well as exposure to immunosuppressive medications. Since the benefits of deceased donor kidney transplantation are clear compared to remaining on renal replacement therapy, the optimum way to assess the risks and benefits is to compare SPK versus deceased donor kidney transplantation alone, versus living donor kidney transplantation alone, and versus PAK.

SPK Versus Deceased Donor Kidney Transplantation Alone

A large registry analysis of 13,467 IDDM patients on the wait list for kidney transplantation and SPK showed that 10-year patient survival was 67% for SPK recipients versus 46% for deceased donor kidney transplant alone recipients (Ojo et al. 2001). The improved patient survival persisted when patients who experienced delayed graft function (which negatively influences post-transplant outcomes) were excluded and occurred despite a twofold risk of early infectious mortality. The latter finding emphasizes the importance of careful patient selection for SPK due to the increased risk of infections compared to kidney transplantation alone. Indeed, the study found that there was no survival benefit for SPK in patients

$\geq$ 50 years of age. This is likely, in part, due to the increased risk of infections in older transplant recipients due to decreased innate immunity with aging. Another study similarly showed that increased recipient age is associated with inferior outcomes after SPK (Bunnapradist et al. 2003).

It appears that in young IDDM patients who are relatively at lower risk of infection, SPK confers an advantage over deceased donor kidney transplantation alone. The benefit occurs at the risk of increased early mortality. It is important to realize that in most areas of the USA, the wait time for a SPK is shorter than a deceased donor kidney transplant alone, further favoring SPK in the carefully selected individual.

SPK Versus Living Donor Kidney Transplantation Alone

The benefit of SPK versus living donor kidney transplantation is not clear. Living kidney donation is associated with superior outcomes compared to deceased donor kidney transplantation and reduces the wait time to receive a kidney transplant. Increased dialysis duration prior to kidney transplantation is known to result in inferior post-kidney transplant outcomes (Meier-Kriesche et al. 2000). The previously described registry analysis of 13,467 IDDM patients did not demonstrate any long-term survival advantage for SPK versus living donation kidney transplant alone, as 10-year patient survival was 67% and 65%, respectively (Ojo et al. 2001). As expected, early post-transplant mortality was less with living donor kidney transplant alone versus SPK. A single center study of 379 SPK recipients versus 130 living related donor kidney transplant recipients did not find a 5 year patient or renal allograft survival advantage (Rayhill et al. 2000).

It appears that the decision to perform SPK versus living donor kidney transplant alone cannot be based on expected patient and kidney allograft survival since these appear to be similar in both groups. Instead, each potential SPK recipient must be carefully evaluated to determine if he/she has factors that favor SPK. Certain characteristics that may favor SPK include young age, absence of cardiovascular or peripheral vascular disease, and brittle diabetes with frequent episodes of hypoglycemic unawareness. Conversely, factors that may favor living donor kidney transplant alone include older age, increased surgical risk (frailty, history of poor wound healing, cardiovascular and/or peripheral vascular disease), long expected wait time for SPK, and well-controlled IDDM with no hypoglycemic unawareness. It is also important to consider that living donor kidney transplantation can preempt the need for dialysis or shorten dialysis duration compared to SPK. Quality of life is significantly improved with successful kidney transplantation compared to remaining on dialysis.

SPK Versus PAK

One of the potential benefits of SPK versus PAK is a single operation for transplantation of both organs. A single operation reduces the risk of an anesthetic complication and only requires a single incision. However, pancreas transplantation in PAK will be done when the patient is not in a uremic state. The uremic patient has a higher likelihood of being malnourished compared to the nonuremic patient. Avoidance of the uremic state will reduce the risk of postoperative bleeding, infections, and electrolyte complications. As described previously, pancreas transplantation is riskier than kidney transplantation alone with an increased risk of postoperative bleeding, wound complications, and infections.

The risk of allograft rejection is felt to be highest in the immediate post-transplant and subsequent peritransplant period. As a result, higher levels of immunosuppression are prescribed at the time of transplantation. A second potential benefit of SPK versus PAK is that only a single round of intensified immunosuppression will be needed as opposed to two rounds of intensified immunosuppression with PAK. In theory, reduced exposure to immunosuppression will decrease the risk of future infectious complications, including opportunistic infections, and malignancies. In addition, one of the mainstays of the immunosuppressive regimen after kidney and pancreas transplantation

is a calcineurin inhibitor. Calcineurin inhibitors are known to be nephrotoxic and the increased levels of this medication required in the immediate and peritransplant period can negatively affect kidney allograft function in PAK.

A third potential benefit of SPK versus PAK is that both transplanted organs are procured from the same donor in SPK. This is important because pancreas and kidney transplant rejection is often concordant in SPK. Early detection of pancreas allograft rejection has historically been more difficult than early detection of kidney allograft rejection. In theory, pancreas allograft survival may be improved in SPK versus PAK since pancreas transplant rejection can be detected and treated at an earlier stage.

Several studies have attempted to determine if the potential benefits of SPK outweigh the advantages of receiving a living donor kidney transplant and, in many cases, reducing dialysis duration with PAK. A single center study compared bladder-drained SPK ($n = 25$) to PAK ($n = 47$) and found that 1 year pancreas allograft survival (92% for SPK, 87% for PAK) and 1 year patient survival (100% for SPK, 93% for PAK) was similar in both groups (Larson et al. 2004). Another single center analysis evaluated 61 PAK patients and 142 SPK patients from January 2003 through November 2007 (Fridell et al. 2009). One year patient survival (98% for PAK, 95% for SPK) and 3 year patient survival (92% for PAK, 88% for SPK) was not statistically different. In addition, 1 year pancreas allograft survival (95% for PAK, 90% for SPK) and 3 year pancreas allograft survival (90% for PAK, 83% for SPK) was not statistically different. The results from these two studies differed from previous studies that suggested that pancreas allograft survival is potentially decreased in PAK versus SPK (Gruessner and Sutherland 2005). The differing conclusions can potentially be explained by the reduced rate of pancreas allograft rejection in the more recent cohort of PAK patients due to better understanding of optimal immunosuppressive management after pancreas transplantation. Regardless, there does not appear to be either a patient survival advantage or disadvantage when comparing SPK to PAK.

In regards to the effects of pancreas transplantation on renal allograft function, a single center study compared renal allograft function, as measured by iothalamate clearance, at 1 year post-pancreas transplant for 17 SPK and 25 PAK patients (Larson et al. 2004). The study found that renal allograft function was significantly lower 1 year post-transplant in PAK patients while remaining unchanged in SPK patients. A multivariate analysis failed to identify the etiology of these findings. The authors hypothesized that higher calcineurin inhibitor levels in PAK versus SPK might be a potential cause but was not found to be significant in their analysis because 1 year calcineurin inhibitor level, rather than an area-under the curve calculation of calcineurin inhibitor exposure, was measured. The results of this study must be interpreted with caution, however, as the number of patients was small and all pancreas allografts were bladder drained. In addition, the follow-up period for renal allograft function was relatively short and the impact of a 1 year decline in renal allograft function on long-term renal allograft survival in PAK recipients is unclear.

It appears as if SPK and PAK are similar in outcomes in regards to pancreas allograft survival and patient survival. It is unclear if long-term renal allograft survival differs with either modality. The decision to perform SPK versus PAK depends on several factors including availability of living donor and wait time for deceased donor pancreas transplant alone versus simultaneous pancreas and kidney transplant. At the transplant center level, living donor kidney transplantation is preferable since it reduces the usage of a scarce resource (deceased donor kidney organ) that should preferably be offered to patients who do not have a suitable living donor.

SPK for Non-Insulin Diabetes Mellitus (NIDDM)

IDDM is felt to primarily be due to insulin deficiency while NIDDM is felt to be secondary to insulin resistance. As a result, pancreas transplantation has historically been reserved for patients with IDDM rather than NIDDM. A United Network for Organ Sharing data analysis from 2000

to 2007 showed that 8.6% of SPKs occurred in patients with NIDDM (Sampaio et al. 2011). In general, the distinction between IDDM and NIDDM at transplant centers has relied upon C-peptide levels, which should presumably be undetectable in IDDM patients. A single center retrospective analysis of SPK patients from 1989 through 2008 stratified by detectable versus nondetectable C-peptide levels demonstrated that there was a trend towards better allograft survival in the detectable C-peptide level group (Light and Tucker 2013). Interestingly, patient survival was significantly reduced in the detectable C-peptide which the authors hypothesized was due to older age at the time of transplant (42.8 years of age versus 38.5 years of age for the nondetectable C-peptide group). Another single center analysis of 21 NIDDM SPK patients revealed that 5 year kidney allograft survival was similar to IDDM SPK patients and superior to NIDDM kidney transplant alone recipients (80.4% for NIDDM SPK versus 83.6% for IDDM SPK versus 52.7% for NIDDM kidney transplant alone) (Margreiter et al. 2013). A scientific registry of transplant recipients analysis found there was not a 5-year survival advantage in NIDDM SPK patients compared to NIDDM kidney transplant alone patients (Wiseman and Gralla 2012). In addition, living donor kidney transplant alone was associated with improved 5 year patient and kidney allograft survival compared to SPK in NIDDM patient. This was in contrast to the similar outcomes noted with living donor kidney transplant alone and SPK in IDDM patients. The decision to perform SPK in NIDDM patients remains controversial but carefully selected patients might benefit from this option. In addition, the benefits of successful pancreas transplantation on quality of life and retardation of secondary diabetic complications were not taken into account in the above mentioned studies.

Conclusion

Pancreas transplantation has the ability to reduce, and in some instances improve, the secondary complications of diabetes mellitus. Achieving normoglycemia can dramatically improve the diabetic patient's quality of life. However, possibly due to the inherent risks of pancreas transplant surgery and of the required immunosuppressive medications, a clear-cut mortality benefit has not been shown with pancreas transplantation.

Pancreas transplant surgery carries a high risk of surgical complications and is associated with more infectious complications than other solid organ transplant surgeries. As a result, the potential pancreas transplant recipient must be carefully selected. Potential risk factors for morbidity and mortality after pancreas transplantation include older recipient age, increased time spent on dialysis, cardiovascular disease, and peripheral vascular disease.

PTA is an option for diabetic patients who do not need a kidney transplant. Mortality risk is potentially increased in the early post-transplant period after PAK, but this risk is decreasing as more experience with pancreas transplant surgery and immunosuppression is gained. PTA should be reserved for diabetic patients who suffer from hypoglycemic unawareness or have "brittle" diabetes despite a maximal coordinated effort between the patient and the diabetic specialist. Islet cell transplantation is another option for patients who are felt to be at higher surgical risk but, unfortunately, is usually not covered by insurance in the USA.

PAK and SPK are options for the diabetic patient who also need a kidney transplant. Neither option has proven to be superior compared to each other or to living donor kidney transplantation alone. Both options appear to be superior compared to deceased donor kidney transplantation alone. The decision to perform SPK or PAK needs to be made on an individual case by case basis. The benefits of SPK for the NIDDM patient are not entirely clear but might provide improved long-term kidney allograft survival and improved quality of life compared to deceased donor kidney transplant alone in carefully selected patients.

Pancreas transplantation should be considered for all patients with IDDM. Early referral is important to prevent the often irreversible and devastating effects of the secondary complications of diabetes mellitus. The transplant center needs to carefully select patients for pancreas transplantation by weighing the benefits of

normoglycemia against the surgical and immunosuppressive therapy risks. The transplant center also needs to help guide the patient in regards to which pancreas transplant option is optimal.

Inclusion Criteria for SPK

1. Type I diabetic
2. Type II diabetic with significant hypoglycemic unawareness
3. Age <55 years
4. BMI <40

Inclusion Criteria for PAK:

Same as SPK and patient must have serum creatinine of < 2 mg/dL or calculated creatinine clearance >40 ml/min

Required Testing for the Potential Pancreas Transplant Candidate

1. Serum C peptide level
2. Annual nuclear stress test or dobutamine echocardiogram
3. Annual 2D echocardiogram
4. Cardiac catheterization strongly recommended for individuals >45 years or diabetes mellitus duration >20 years
5. Routine transplant testing (e.g., chest x-ray, EKG, CMP, CBC, PTT, PT/INR, hepatitis B and C panel, HIV serology, PPD, EBV IgM/IgG, CMV IgG/IgM, PAP smear if female of reproductive age, mammogram if female age 40 or higher, PSA if male age 50 or higher, colonoscopy if age 50 or higher)
6. Transplant surgical evaluation of peripheral circulation

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Diabetes Mellitus: Diagnosis and Care

Joseph Giangola

Contents

Abstract

Diabetes is an increasingly common disease which is encountered in the surgical patient. Poor control of blood glucose makes poor outcomes such as surgical site infection more common. There is now an abundance of literature describing surgical outcomes in diabetic patients in all subspecialties. Effective use of inpatient resources is more essential than ever in inpatient care with the drive for cost-effective and evidence-based care. It is important to distinguish type 1 from type 2 diabetes in management while in the hospital. A large number of oral agents are available to treat type 2 diabetes along with different insulin preparations, and a knowledge of them will help the surgeon especially in the transition to

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rehab or home care. While in the hospital insulin is the best course, either an infusion or a conventional subcutaneous regimen will need to be employed. Protocols and inpatient order sets are essential in the proper management of the patient with diabetes while in the hospital.

Keywords
Diabetes incidence · Insulin infusion · Type 1 diabetes · Type 2 diabetes · Diabetes complications · Length of stay · Preoperative workup · Neuropathy · Oral agents · Insulin preparations · Sliding scale · Intensive care · Transition to subcutaneous insulin · Special situations

Introduction

At any large medical center in the USA, one is likely to find that anywhere from 12% to 20% of the inpatient population will be diabetic, in both medical and surgical areas. Patients with diabetes are found throughout the hospital, from mother baby to cardiac surgical ICU. There is no surgical subspecialty in which diabetes is not encountered. At the present time there are about 20.9 million people with diabetes and about nine million undiagnosed in the USA (Centers for disease Control and Prevention 2014). It should be noted that diabetes is a global problem and not just limited to the USA with increasing incidence most notably in India and China. It has been estimated that a diabetic person has a 25% lifetime risk of requiring some type of surgical procedure. There is a large and growing body of literature documenting differences in outcomes in diabetic surgical patients. Most studies simply report association of hyperglycemia in diabetic patients, as well as those without, with poorer outcomes and increased length of stay; it almost doesn't matter which surgical subspecialty is looked at (AACE and ADA 2009; Preoperative blood glucose… 2014; Preoperative A1c… 2014; Frisch et al. 2010). As an example, in 2010 73,000 nontraumatic lower limb amputations in diabetic patients were carried out in the USA. Patients with diabetes stay longer in the hospital, cost more to take care of, and have higher morbidity and mortality than those without (Preoperative A1c… 2014). Vascular surgery in particular has received a great deal of attention (2009; O'Sullivan et al. 2006a). In orthopedic surgery there is an abundance of literature documenting the association of uncontrolled blood glucose and poor outcomes (Stryker et al. 2013). Surgical oncology data has also looked at this issue with similar findings (Wei et al. 2014). All medical centers and hospitals in the USA are seeking ways of delivering the same quality of care at a lower cost due to changing reimbursement, and diabetic patients are one group in which expenditures for care are very significant. Reviews and recommendations have been published (AACE and ADA 2009). A systematized method of caring for them is essential (AACE and ADA 2009; Joshi et al. 2010).

Why Is Glucose Control Important in Care of the Diabetic Patient?

What one hopes to accomplish in perioperative diabetes care is straightforward: an improvement in the outcome of the particular surgery, a reduction in morbidity and mortality, and perhaps a reduction in length of stay with a consequent reduced cost in care. There is no question that inpatient hyperglycemia leads to worse outcomes. In an ideal world an elective surgery patient with diabetes would be referred to a surgeon for a decision on whether surgery is necessary. The patient would be sent back to the primary care provider to prepare for the intervention with specific instructions regarding diabetes medications and/or insulin. If that patient was deemed to have suboptimal control, he or she would be referred to a diabetes specialist who could better prepare the patient for surgery with a changed diabetes regimen (Dhartariya et al. 2012). Postoperative care would be then tailored to the patient based on his means of control before the surgery and then discharged to resume usual care. This could serve as a standard that could inform the care of the emergent patient for whom this is not possible. Unfortunately this is not the case a good portion of the time.

More than two decades ago, the Diabetes Control and Complications Trial (Harris et al. 1994) firmly established that good control in type 1 diabetic outpatients could reduce diabetes-specific complications such as retinopathy, neuropathy, and incipient nephropathy with a trend to reducing CAD. This study was done in outpatients. Evidence-based proof that inpatient control was equally beneficial would come later. This is true whether the patients are known diabetics, prediabetic, or experiencing stress hyperglycemia. The first study showing a benefit from better glycemic control was in post-cardiac bypass patients. Furnary et al. in 1999 simply ran an insulin infusion in their post-CABG to obtain relatively modest control of hyperglycemia patients, and they substantially reduced sternal wound infections (Furnary et al. 1999). Evidence for the beneficial effect in ICU patients was provided by the Van den Berghe study which was published in 2001. It showed that tight glycemic control in intensive care diabetic patients reduced several complications significantly (Van den Berghe et al. 2001). This study radically changed the landscape as far as attitudes toward inpatient control were concerned. Recommendations were developed from this study quickly changed the approach to treating hyperglycemia in critically ill patients. Several years later the NICE-SUGAR trial, designed to test the hypothesis that tight control could lead to improved outcomes, seemed to indicate the opposite. In that trial, patients very tightly controlled in intensive care units did more poorly in terms of survival at 6 months (2009). A whole host of factors could have contributed to discrepant findings such as different protocols, different goals, different methods of measuring blood glucose, etc. (2012). This led to a reconsideration of goals and will be discussed further down.

Underlying Pathophysiology

Surgical stress which in turn leads to the release of counterregulatory hormones such as cortisol, catecholamines, growth hormone, and glucagon each of which can result in hyperglycemia. It is possible that this response is, to some degree, adaptive. In type 1 diabetes, with absolute insulin deficiency, and type 2, with relative deficiency, an even greater rise in glucose levels is seen than in normal individuals. Both general and local anesthesia can raise blood glucose though the former is more likely. A large number of factors contribute to the differences in surgical outcome in diabetic patients. The normal function of vascular endothelium is altered by hyperglycemia, neutrophil function is impaired, cytokine synthesis is increased, and inflammation is worsened. All of these can interfere with wound healing. Hyperglycemia can cause dehydration and predispose to infection by altering immune function. Leukocyte function is impaired on exposure to hyperglycemia, inflammation may be triggered, and endothelial function may be adversely affected (Therapy for diabetes mellitus and related disorders). Hyperglycemia has adverse effects on the vascular endothelial function (Dandona 2002).

Evaluating the Patient

Identifying and characterizing the patient admitted to the hospital is the first step. The simple addition of the diagnosis or even the use of antidiabetic medications should trigger interventions in the hospitalized patient such as the automatic monitoring of blood glucose among other things. An adult patient with type 2 diabetes will be managed differently in some respects than the patient with type 1. The differences are noted below (Table 1).

The diagnostic criteria for diabetes are listed in Table 2.

Rationale and Means of Distinguishing Type 1 and Type 2 Diabetes

Type 1 diabetes is an autoimmune disorder characterized by complete or nearly complete absence of insulin production. The diagnosis of type 1 diabetes is generally in the adolescent years. This is useful when obtaining a history in that one can be fairly certain that a patient is insulin dependent based on the age at onset, but true type 1 diabetes

Table 1 The two major types of diabetes and distinguishing characteristics

Type 1 diabetes	Onset during childhood or adolescence and less commonly at older ages About 5% of diagnosed diabetes in the USA More common in Caucasians Autoimmune in nature and accompanied by conditions, i.e., thyroid disease and celiac disease Insulin deficient and needing continual insulin provision
Type 2 diabetes	Onset generally in adulthood and accounting for 90–95% all diagnosed diabetes in the USA and increasing incidence with age Insulin resistant *and* deficient and may need insulin as outpatient Accompanied very frequently by hypertension, obesity, elevated triglycerides, and a sedentary lifestyle More common in ethnic minorities

Table 2 Diagnosis diabetes (Hypoglycemia and the risk. . . 2014)

Q1. How is diabetes screened and diagnosed?

Diagnostic Criteria for Prediabetes and Diabetes in Nonpregnant Adults

Normal	High Risk for Diabetes	Diabetes
FPG <100 mg/dL	IFG FPG ≥100-125 mg/dL	FPG ≥126 mg/dL
2-h PG <140 mg/dL	IGT 2-h PG ≥140-199 mg/dL	2-h PG ≥200 mg/dL Random PG ≥200 mg/dL + symptoms*
A1C <5.5%	5.5 to 6.4% For screening of prediabetes†	≥6.5% Secondary‡

*Polydipsia (frequent thirst), polyuria (frequent urination), polyphagia (extreme hunger), blurred vision, weakness, unexplained weight loss.

†A1C should be used only for screening prediabetes. The diagnosis of prediabetes, which may manifest as either IFG or IGT, should be confirmed with glucose testing.

‡Glucose criteria are preferred for the diagnosis of DM. In all cases, the diagnosis should be confirmed on a separate day by repeating the glucose or A1C testing. When A1C is used for diagnosis, follow-up glucose testing should be done when possible to help manage DM.

FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; PG, plasma glucose.

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can develop in middle age and even in the elderly though much less commonly. Other autoimmune disease such as hypothyroidism and celiac disease (among other conditions) may also be present as well and serve as an indicator where it is uncertain (Therapy for diabetes mellitus. . .). Rarely a surgical emergency such as appendicitis will lead to the detection of hyperglycemia and subsequently, type 1 diabetes. Each of these will have some bearing on management of the patient both pre- and postoperatively. Insulin is essential and must be provided throughout the stay. The current standard of care in type 1 diabetes is intensive insulin therapy which almost always employs insulin analogues: both long acting and short acting. Many patients, however, still use regular, NPH, and premixed 70/30 preparations. This is particularly true in uninsured patients or those who are

unable to pay for the newer and more expensive analogues. Insulin is preferred in the hospital for various reasons. More patients are using insulin pumps especially in the last decade to deliver insulin, though most are on multiple-dose insulin regimens that will be discussed further down.

Type 2 diabetes is characterized by both insulin deficiency and insulin resistance (Therapy for diabetes mellitus. . .). It is possible that the latter leads to the former over time though this is debated. Onset occurs usually in midlife in overweight and sedentary adults, although it is now even being seen in adolescents (particularly in African American and Hispanic patients). Type 2 diabetic patients very frequently have hypertension and dyslipidemia. These two conditions predispose the patient to vascular disease, again influencing strongly the inpatient management plan. Blood glucose is controlled by oral agents, oral agents plus injectable agents like incretin mimetics (exenatide, liraglutide, albiglutide, and dulaglutide; see below), oral agents plus insulin, or insulin alone.

A thorough history and physical is necessary in view of the incidence of cardiovascular, renal, and neurologic disease in diabetes. Preoperative workup must include assessment for the presence of these conditions. Renal disease may complicate both fluid replacement and electrolyte balance. Prior EKGs, cardiac catheterization results if available, BUN, creatinine, and potassium should be on the chart and done within the past month according to most protocols for pre-op evaluation. An A1c hemoglobin on admission or within a few months of the procedure is recommended (AACE and ADA 2009). Diabetic patients can be considered at the same operative risk as those with known cardiovascular disease (Kuusisto and Lassko 2013). Severe peripheral arterial disease coupled with neuropathy can result in a foot ulcer developing in a patient admitted for coronary revascularization or any prolonged hospitalization with bed rest. Neuropathy which can be elicited in the history or on a physical exam may also increase risk for hemodynamic instability or cardiac arrhythmia. Diabetic arthropathy causes limitation of joint mobility and may even make endotracheal intubation difficult. It should be added that, in keeping what was already said about the challenge of controlling costs, a heel ulcer that develops during an admission may not be reimbursed leading to the medical center having to absorb the extra expense in total care. Nothing can substitute for good clinical judgment from a physician experienced in the care of inpatient diabetes.

Special attention must be given to the patient with type 1 diabetes. C*ontinual provision of insulin is necessary.* This is why the type 1 diabetic patient simply will do best through a surgical hospital stay with a consult by an endocrinologist or internist skilled in the care of diabetes. If the patient has required an insulin infusion to maintain control and needs to be transitioned to subcutaneous therapy, this is particularly true. The patient's knowledge of how they respond to insulin and what doses they usually will need is often neglected in preoperative histories. People with type 1 diabetes have a good idea as to how insulin sensitive they are. Often larger doses are given than is necessary, especially once the immediate surgical stress response has abated. The uncomplicated and usually young type 1 patient requires only attention to insulin provision beyond usual surgical care. This may also be true of the short duration older type 2 patient.

Oral Agents Available for the Treatment of Diabetes

Knowledge of outpatient treatment regimens is useful in managing the diabetic patient. A number of new oral medications have been recently introduced for the treatment of type 2 diabetes. It can be a confusing and daunting task to accurately document all medications being taken at admission. Getting a grasp of how they are used requires a brief review of the pathophysiology. An excellent review of oral agents was created by the American Diabetes Association (Therapy for diabetes mellitus and related disorders). The basic causes of type 2 diabetes have been described as the "ominous octet" according to DeFronzo (2009; Taber et al. 2013). The diabetic patient may completely lack insulin as in autoimmune type 1 diabetes

Table 3 Oral agents used in the treatment of diabetes

Major drugs used in the treatment of type 2 diabetes			
Drug class	Mode of action	Cautions/side effects	Perioperative use
Sulfonylureas glyburide glipizide glimepiride	Stimulate release of preformed insulin from beta cells	Hypoglycemia in those renal, hepatic, severe CHF, malnutrition, and elderly	Hold preoperatively. May restart when stable and eating with monitoring for hypoglycemia
Brigands Metformin	Reduce hepatic glucose output and increase insulin sensitivity	Lactic acidosis risk in those with renal disease. D/C for 48 h ours after contrast dye. Hold for creatinine >1.5 male and 1.4 female Will not cause hypoglycemia used alone	Hold perioperative. May restart when stable and creatinine normal
Thiazolidinediones Pioglitazone (Actos) Rosiglitazone	Insulin-sensitizing drugs with slow onset of action	Avoid with CHF, liver disease, edematous states No hypoglycemia used alone	Delayed onset of action
DPP-IV inhibitors Sitagliptin (Januvia) Saxagliptin (Onglyza) Linagliptin (Tradjenta) alogliptin (Nesina)	Inhibit breakdown of GLP-1 by DPP-IV in blood and stimulate insulin secretion if glucose abnormal, reduce glucagon levels	Avoid with prior history of pancreatitis. Doses need to be reduced with all but linagliptin No hypoglycemia used alone	May be restarted when patient restarts diet
Incretin mimetics Exenatide (Byetta, Bydureon) Liraglutide (Victoza) Albiglutide (Tanzeum) Dulaglutide (Trulicity)	Injectable drugs that directly act like GLP-1 with stimulation insulin release when glucose level abnormal, reduce glucagon, slow gastric emptying, promote satiety	Avoid with prior hx pancreatitis or thyroid C-cell cancers, any situation in which gastric emptying might be delayed. Will not cause hypoglycemia used alone	Not for use in hospital at this time
Alpha-glucosidase inhibitors Acarbose (Precose) Miglitol (Glyset)	Partially block the breakdown of polysaccharides in the gut and slowing glucose absorption	GI side effects such as gas and bloating. If used with other agents and hypoglycemia occurs, must give glucose to correct	Avoid use in hospital

which renders the treatment fairly straightforward insulin replacement. In type 2 diabetes, a patient will have beta cell failure to varying degrees accompanied by resistance to the glucose-lowering effect of insulin. This resistance occurs at the level of the liver, muscle, and fat. The patient may also lack the so-called gut hormones that help to lower glucose through reduction of glucagon and the slowing of gastric emptying among other effects. Not long ago it was also shown that the type 2 diabetic patient reabsorbs excess glucose in the kidney. Oral agents are available to combat each of these defects (as well as others not mentioned such as increased lipolysis from adipose tissue and insulin resistance in the CNS.) In outpatient treatment considerations other than straightforward glucose lowering have to be taken into account. This is not the case for inpatient treatment where insulin is the favored method of control. The table below summarizes oral meds available with brief recommendations for their use in the perioperative setting. It leaves out a few agents that are used very infrequently such as bromocriptine (Cycloset) (Table 3).

Sulfonylureas (SUs) are the oldest oral agents having been introduced in the 1950s. The mechanism of action essentially involves stimulation of the release of insulin from the beta cell and can therefore be referred to as insulin secretagogues. There remains concern that these agents increase cardiovascular risk, but they are still widely used because of their effectiveness and low cost. The three main SUs used will be glyburide, glipizide, and glimepiride. Glyburide has the longest plasma half-life, has active metabolites, and is excreted equally in the urine and feces. It is probably the agent with the most potential for causing hypoglycemia and ought to be eliminated from the hospital formulary. Both glipizide and glimepiride have shorter half-lives, are inactive metabolites, and are excreted in the urine and feces (though 80% of glipizide is eliminated in the urine). The chief concern in using these agents is hypoglycemia. This is particularly true if they are continued in the hospital in the surgical patient where intake will be interrupted or unreliable or the patient may be NPO. Therefore their use is discouraged in hospitalized diabetic patients, both surgical and medical.

Short-acting secretagogues such as repaglinide and nateglinide (Prandin and Starlix, respectively) act in a similar fashion as the SUs. The same advice applies to their use in the hospital as the SUs; try to avoid them.

Metformin is the most widely used oral agent for the control of type 2 diabetes and is nowadays almost always the first oral agent to be used in the newly diagnosed patient. It will be found in an admitted diabetic patient's medication list frequently. Metformin is used alone and in combination with SUs both glyburide and glipizide (Glucovance and Metaglip) as well as in combination with a thiazolidinedione (ActoPlus Met) and the DPP-IV class described below (Janumet, Jentadueto, Kombiglyze, and Kazano). It will not cause hypoglycemia when used by itself. The value of metformin is its mechanism of action. This includes reduction of insulin resistance, reduction of fasting glucose by suppression of hepatic glucose production, and improvement of the lipid profile. Metformin has been combined with sulfonylureas, DPP-IV agents, thiazolidinediones, and SGLT2 inhibitors with a bewildering array of names. By itself and in combination, it should be avoided in severe liver disease and in alcoholics. Lactic acidosis is a serious and rare side effect with its use. The chief limitation to the use of metformin is renal disease, though it may also present a danger in any CHF, respiratory failure, sepsis, or any condition causing hypoxia. It should also be avoided in severe liver disease and in alcoholics. The safest thing to do with metformin in the diabetic patient in the perioperative period is to stop it and only restart it when the patient is clearly stable and eating and kidney function is normal. However, recommendations on metformin use may be changing in the near future (Duncan et al. 2007).

Keeping in mind that the pathogenesis of type 2 diabetes involves both insulin resistance and insulin deficiency, the only oral agent that targets the former still in wide use is the thiazolidinedione (TZD) pioglitazone (Actos). Rosiglitazone (Avandia) use essentially stopped with suggestions that it increased risk of cardiovascular events (Nissen and Wolski 2007). While there are several biologic effects of pioglitazone involving lipid metabolism mainly, its main action is to reduce insulin resistance. When used in an outpatient, it generally requires a few weeks for its full effects to be seen. The main adverse events are fluid retention, weight gain, and edema. It can precipitate CHF when subclinical disease is present. An increased incidence of small bone fractures has been observed as well. Use in the hospital is not practical for the delayed action as well as for edema and CHF.

The alpha-glucosidase inhibitors are an infrequently used class of oral antihyperglycemic agents. They block the absorption of complex carbohydrates by slowing their digestion. The two agents commonly used are acarbose (Precose) and miglitol (Glyset). They competitively inhibit the brush border enzymes in the intestine. They effectively lower blood glucose concentrations and can be used in combination with other agents such as metformin or SUs. If used with SUs and hypoglycemia occurs, glucose, not sucrose or fructose, must be used to reverse symptoms. The chief side effects are gastrointestinal and consist of bloating and gas.

Carbohydrate taken orally induces not just the secretion of insulin from pancreatic beta cells but also the production of intestinal hormones that help control blood glucose. This is called the incretin effect and largely is due to the secretion of glucagon-like peptide 1 (GLP-1) from L cells in the distal small intestine and colon. Secretion of GLP-1 is deficient in type 2 diabetic just like insulin deficiency is present. GLP-1 is rapidly degraded by dipeptidyl peptidase-4. Inhibition of this enzyme results in prolonged action of GLP-1 and greater stimulation of insulin secretion with consequent reduction of blood glucose levels. The efficacy of these agents is a bit less than metformin or the SUs used as monotherapy. They work well in combination with metformin. Their chief advantage is that they do not cause weight gain or hypoglycemia. This last feature makes them particularly useful in the geriatric population. If an older surgical patient comes in on an SU and has had significant weight loss, renal, or cardiac issues, discharging them on a DPP-IV is often a good and safe choice. The agents are listed as follows: sitagliptin (Januvia), linagliptin (Tradjenta), saxagliptin (Onglyza), and alogliptin (Nesina). Each of them, as noted above and respectively, is marketed in combination with metformin. Obviously the caveats that apply to metformin do also apply to the combinations. There may be a use for a DPP-IV in the hospital as one pilot study has shown (Umpierrez et al. 2013).

The DPP-IV inhibitors prevent the degradation of GLP-1 thus controlling blood glucose as noted above. It is also possible to directly provide GLP-1 mimetics. They are given by injection either on a daily or weekly basis. They increase insulin secretion, decrease glucagon secretion, slow gastric emptying, and exert an effect of the CNS to reduce food intake. Their effect on weight loss is significant and has led to the recent approval of the use of one of them (liraglutide) for weight reduction. Pancreatitis is still listed as a potential risk with these agents. The ADA and AACE have stated that the product labeling indicating this should remain as stated and treatment of patients with these agents should continue. To this date pancreatic cancer is not convincingly related to the use of GLP-1 mimetics. They can cause nausea, though this side effect is not related to the degree of weight loss. Allergy can occur as well. While their use in the hospital has been investigated, they are outpatient treatments (Kaneko and Sato). Exenatide can be used twice daily as Byetta and weekly as Bydureon and liraglutide used daily as Victoza, albiglutide as Tanzeum, and dulaglutide as Trulicity. Liraglutide has been used in elective surgical patients in at least one limited study so may have a role in the future.

Insulin Preparations

Insulin is the preferred agent used to control hyperglycemia in the hospital. A long-lasting insulin is extremely useful in surgical patients. Glargine and detemir (Lantus and Levemir, respectively) both have longer durations of action and are "flatter" in their pharmacodynamic effects without the peaking that occurs with the use of NPH or regular insulin. For opposite reasons, the rapid-acting analogues lispro, aspart, and glulisine are preferred over the standard regular insulin because of their shorter duration, rapid peaking in patients who are eating, and more predictable effects. Listed below are the commonly available insulin preparations (Table 4).

Hypoglycemia

Hypoglycemia was alluded to above as a concern in the control of perioperative patients. It has been implicated in increased mortality in some reviews (Hypoglycemia and the risk… 2014). It has also been associated with longer length of stay, increased mortality and morbidity, and increased rate of readmission (Zapatero et al. 2014). Hypoglycemia may be a marker for illness or an indicator of severity of illness. Concise recommendations on the issue have been well described (Eiland et al. 2014). The guidelines listed below address maintenance of a safe range both in and out of the intensive care units.

Table 4 Major types of insulin and characteristics

Insulin	Onset of action[a]	Peak	Duration
Regular	30–60 min	2–3 h	6–8 h
Lispro (Humalog)	15–30 min	1–2 h	3–5 h
Aspart (Novolog)	15–30 min	1–2 h	3–5 h
Glulisine (Apidra)	15–30 min	1–2 h	3–5 h
NPH			
Glargine (Lantus)	60–120 min	"Peakless"	Up to 24 h[b]
Detemir (Levemir)	60–120 min	"Peakless"	12–18 h[b]
Humulin or novolin 70/30	30–60 min	4–8 h	10–16 h
Humalog or novolog 70/30	15–30 min	4–8 h	10–16 h

[a]Times given are only approximate and vary depending on various patient-specific factors. In practice, the rapid-acting analogues are used interchangeably

[b]Both basal insulin preparations can vary, but glargine is generally longer lasting than detemir. Detemir may best be given twice daily especially in type 1 diabetic patients

Goals of Control

Hyperglycemia in the hospital is defined by any blood glucose greater than 140. There are basically three groupings of hyperglycemic patients. Stress-induced hyperglycemia occurs in patients without diabetes and is generally self-limiting to the period of severe illness. Prediabetic patients are in a gray zone where glucose values are not frankly abnormal.

Generally, treatment for elevated glucose levels should start at 180 with a goal of 140–180 mg/dl. Noncritically ill patients ideally should have fasting and premeal <140 with random values of <180. Goals can be modified based on the patient's status. For those with limited life expectancy or terminal illness, less strict values are acceptable, and avoidance of dehydration and electrolyte imbalance is the main consideration. Tighter control can be attempted if it can be achieved safely, i.e., without glucose values <70. Hypoglycemia itself may be harmful and a number of factors predispose the patient. They include renal failure, poor or interrupted intake, sepsis, malnutrition, liver disease, and of course the use of insulin. The harm may come primarily from cardiac causes and is evident both in hospital and out (AACE and ADA 2009).

But first, a word about capillary glucose testing. The FDA has ruled recently on their use in the critical care setting stating that the accuracy for patient management is insufficient (48). However, most clinicians believe that the use of insulin infusions in the intensive care units as well as treatment of noncritically ill patients would be impossible without the use of this technology (Jacobi Critical Care Med 2012. Vol 40, no 12). Regular medical and surgical patients on the floor may show misleading results with possible harm to the patient if the values are acted on. Physicians and nurses have taken this into account and usually recheck a finger stick or ask for a confirmation from the laboratory. The use of insulin infusions in the intensive care units as well as treatment of noncritically ill patients would be impossible without the use of this technology. The relevant patient factors that could lead to inaccurate results are low hematocrit (overestimation of true glucose) and drugs/dietary supplements. Acetaminophen and ascorbic acid are well-known instances, but high bilirubin or uric acid may also interfere. Hypotension, vasopressor use, edema, and hypoperfusion may also be significant. Therefore, caution must be the byword in interpreting the glucose results for patients with any of these drugs or clinical states. Confirmation should be periodically obtained with simultaneous lab testing keeping in mind differences between venous, arterial, and capillary blood.

Strategies for Control

NICE-SUGAR caused most institutions to exercise greater caution and to abandon the tight goals set after the Van den Berghe study. The ADA has strongly recommended easy-to-use and straightforward protocols that surgeons and anesthesiologists can quickly implement. The fact that many institutions do not have these in

place is an obstacle to achieving better control (AACE and ADA 2009).

Intensive Care Setting

In critically ill patients treatment should be started at 180 mg/dl with a target range of 140–180. Many units can maintain 100–150 with a low level of hypoglycemia. Most protocols include a 1:1 ratio of 1 unit per 1 ml and are delivered with an infusion pump. Hourly glucose values till in range and then every 2 h testing is sufficient to ensure control. Subcutaneous sensors are commercially available and in use by patients at home but have the same limitations that capillary glucose measurements do presently and, until more studies are done, are not recommended. Many insulin infusion guidelines have been published. As stated previously, the best are those that are developed locally with full buy in from all the stakeholders involved. There are advantages and disadvantages for both computerized order sets and for computer algorithm-driven methods. Below is an order set that has resulted in good control as defined by percentage of values within acceptable range and low rate of hypoglycemia (Figs. 1 and 2).

Once control of hyperglycemia has been achieved and the patient is ready to start eating and *transition to subcutaneous insulin,* a protocol should be employed. Below is a summary of various recommendations (Table 5).

A simple plan is summarized below. The inclusion/exclusions speak for themselves:

Guidelines for Transitioning From an Insulin Infusion to Subcutaneous Insulin in Critically Ill Patients with Diabetes in MICU, CCU, and SICU

Inclusions (Must Meet All Three Criteria)

1. Patients with type 2 DM on oral diabetes medications or insulin prior to hospitalization
2. Insulin infusion dosage > 1 unit/h for the 6 h prior to transition
3. Patients tolerating enteral feedings or an oral diet

Exclusions (Any One of the Following)

1. Type 1 DM: requires an endocrine consult for transitioning to long-acting insulin
2. CrCl < 30 mL/min
3. Hemodynamic instability requiring vasopressor use
4. High-dose corticosteroid therapy
5. Stress hyperglycemia (no prior history of DM)

Goal: Achieve a blood glucose of < 180 mg/dL during the 24 h transition

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Calculating Insulin Requirements:

Steps to Calculate the Long-Acting Insulin Dose (Insulin Glargine Preferred)

1. Review the hourly dosing of insulin infusion (units/h) for the last 6 h.
2. Add up the amount of units required in the past 6 h and then multiply it by **four** to quantify total 24 h daily requirement.
3. Administer 50% of the 24 h requirement in the form of long-acting insulin (e.g., insulin glargine).
4. Discontinue insulin infusion 2 h after the administration of long-acting insulin.
5. **Note:** Long-acting insulin may be administered at any time of the day – change the default setting in EPIC to the time of order entry.

Steps to Calculate the Premeal Insulin Dose

1. Continuous enteral feeding: Initiate standard-dose or high-dose corrective **regular** insulin ("sliding scale regular insulin"). Regular insulin is desired in this setting only due to its longer duration of action.
2. Oral diet/bolus feeding: Initiate standard-dose or high-dose corrective **lispro** insulin ("sliding scale lispro insulin").
3. **Note**: Patient's insulin resistance determines whether to initiate standard-dose or high-dose corrective insulin.

Monitoring

1. Enteral feeding: Monitor point-of-care glucose every 6 h.
2. Oral diet/bolus feeding: Monitor point-of-care glucose AC and HS.

ADULT INSULIN INFUSION PROTOCOL FOR SURGICAL ICU AND CARDIAC SURGERY ICU

Criteria for Use of Insulin Infusion in the ICU:

- Patients admitted to an adult Surgical ICU with 2 consecutive blood glucose measurements exceeding 150 mg/dL
- Type 2 Diabetic and non-diabetic patients
- **DO NOT USE** in patients with DKA OR Type 1 Diabetes
- Consult diabetologist/endocrinologist for patients with Type 1 Diabetes prior to utilizing this order set
- **NOT** recommended for use in patients who are receiving PO diet or intermittent bolus feeding

NOTE: The recommendations for titration of an insulin infusion in the ICU provide general guidelines for insulin titration in the ICU population; however, patient's individual sensitivity to insulin, concomitant circumstances (e.g. steroid administration, vasopressor use, hypokalemia, etc.) may affect a patient's response to insulin and should be taken into consideration prior to each titration

1. **REGULAR INSULIN 100 units/100 mL NS IV titrate to ICU BLOOD GLUCOSE (BG) GOAL: 100-150**
2. **Initial Insulin Infusion Rate:** Begin infusion based on the last BG measurement as per diabetic status:

Non-Diabetic Initial Rate:

150-200	201-250	251-300	301-350	351-400	> 400
1 units/h	2 units/h	3 units/h	4 units/h	5 units/h	6 units/h

Type 2 Diabetic Initial Rate:

150-200	201-250	251-300	301-350	351-400	> 400
2 units/h	4 units/h	5 units/h	6 units/h	7 units/h	8 units/h

3. **Administration Guidelines:**
   - ☒ Administer insulin via infusion pump through a dedicated line whenever possible. If not possible, Y-site with **maintenance fluid** or other compatible **continuous** infusions only
   - ☒ DO not stop the insulin infusion for the intermittent infusion of other medications whenever possible
4. **Blood Glucose & Electrolyte Monitoring:**
   - ☒ **Check BG via fingerstick at a minimum of every 2 hours during insulin infusion; after discontinuation of insulin infusion continue to check every 2 hours for a total of 6 hours unless hypoglycemia occurs or PO intake resumes**
     - For BG < 70 mg/dL, increase frequency of BG monitoring q 15 minutes and follow treatment recommendations as per titration guidelines
     - Venous sampling is acceptable, fingerstick sampling is preferred
   - ☒ **Post cardiac surgical patients, check BG q 1 h post operatively until BG within goal range then q 2 h**
   - ☒ Baseline serum potassium (K^+) prior to initiating infusion and at least once daily throughout infusion
5. **Interruption or Discontinuation of Insulin Infusion:**
   - ☒ Hold insulin for BG ≤ 70 and increase frequency of monitoring as per titration guidelines
   - ☒ For interruptions in enteral or parenteral nutrition, continue to monitor BG q 2 h and resume insulin infusion when BG exceeds150 mg/dL based on caloric intake:
     - Resume insulin infusion at the previous rate one hour after full continuous enteral feeding has been restarted
     - Resume insulin infusion based on Initial Insulin Infusion Rate (as above) if enteral feeding is restarted at a decreased rate or the patient remains NPO
   - ☒ Consult prescriber for insulin management during temporary transfers off the ICU when anticipated duration > 1 hour
   - ☒ Upon discontinuation of insulin infusion:
     - If NPO, monitor BG q 2 h X 6 hours, then BG q 6 h if continued NPO or continuous tube feeding
     - Once PO intake resumes, change BG monitoring to AC & HS (pre-prandial)

Fig. 1 Adult insulin infusion protocol for surgical ICU and cardiac surgery ICU

GUIDELINES FOR TITRATION OF INSULIN INFUSION IN THE SURGICAL INTENSIVE CARE UNIT

- Round insulin rates up or down to the nearest 0.5 unit increment
- Consult prescriber for insulin rate exceeding 15 units/hour

If BG ↓ by ≥ 100 mg/dL in 2 h during the insulin infusion, decrease insulin rate by 50%. Recheck BG q 30 minutes until rate of decrease is < 50 mg/dL in 30 minutes, then resume titration schedule based on BG

Current BG (mg/dL)	Rate of Change BG (mg/dL)	CURRENT INSULIN RATE 0.5-5.5 units/h	6-10.5 units/h	11 -15 units/h
> 400		↑ by 2 - 3 units/h	↑ by 3 - 4 units/h	↑ by 4 - 6 units/h
301-400	If BG decreases by ≥ 75 in 1-2 h from prior BG:	↓ by 0.5 unit/h	↓ by 2 - 3 units/h	↓ by 3 - 4 units/h
	If BG increases, no change or decrease by< 75 in 1-2 h:	↑ by 1 - 3 units/h	↑ by 2 - 3 units/h	↑ by 3 - 4 units/h
201-300	If BG decreases by ≥ 50 in 1-2 h from prior BG:	↓ by 1 unit/h	↓ by 2 - 3 units/h	↓ by 3 - 4 units/h
	If BG increases, no change or decreases by< 50 in 1-2 h:	↑ by 0.5 - 2 units/h	↑ by 1 - 3 units/h	↑ up to 1 - 4 units/h
181-200	If BG decreases by ≥ 50 in 1-2 h from prior BG:	↓ by 1 unit/h	↓ by 1.5 - 3 units/h	↓ by 3 - 4 units/h
	If BG increases, no change, or decreases by < 50 in 1-2 h:	↑ by 0.5 - 2 units/h	↑ by 1 - 2 units/h	↑ up to 1.5 - 3 units/h
151-180	If BG decreases by ≥ 20 in 1-2 h from prior BG:	↓ by 1 units/h	↓ by 1 - 3 units/h	↓ by 3 - 4 units/h
	If BG increases, no change, or decreases by < 20 in 1-2 h:	↑ by 0.5 - 2 units/h	↑ by 0.5 - 1.5 units/h	↑ up 1 - 2 units/h
100 -150 GOAL	If BG decreases by ≥ 10 in 1-2 h from prior BG:	↓ by 0.5 - 2 units/h	↓ by 1 - 3 units/h	↓ by 3 - 4 units/h
	If BG increases, no change, or decreases by < 10 in 1-2 h	No Change, ↑ OR ↓ by 0.5 - 1 units/h	No Change, ↑ OR ↓ by 0.5 - 1 units/h	No Change or ↑ by 0.5 - 2 units/h

BG (mg/dL)	INTERVENTION	MONITORING	RESTART infusion when BG > 150, use the previous rate of infusion and decrease by the # of units indicated in the corresponding column and row below: 0.5-5.5 units/h	6-10.5 units/h	11 -15 units/h
81-99	If BG↓ by ≤ 20 in 1-2 h from previous BG, decrease rate by # of units indicated in the corresponding row to the right.	Recheck **60 minutes** until BG > 100, then q 1 h x 1, then q 2 h	↓ by 0.5 -2 unit/h	↓ by 1-2 unit/h	↓ by 2-3 units/h
71-80	If BG ↓ by > 20 in 2 h from previous BG: **HOLD INSULIN**	Recheck **30 minutes** until BG > 100, then q 1 h x 1, then q 2 h	↓ by 0.5 - 2 units/h	↓ by 2 -3 units/h	↓ by 5 units/h
60-70	**HOLD INSULIN** administer D50% 25mL (1/2amp) IVP q 15 min until BG > 100	Recheck **every 15 minutes** until BG > 100, then q 1 h x 2, then q 2 h	↓ by 0.5 - 2 units/h	↓ by 2- 5 units/h	↓ by 5 -7 units/h
50-59	**HOLD INSULIN** administer D50% 25mL (1/2amp) IVP, recheck BG in 15 min, repeat D50% 25 mL if BG < 100. If BG is persistently< 70 after D50% x 2, contact prescriber				
< 50	**HOLD INSULIN** administer D50% 50mL IVP, recheck BG in 15 min, repeat D50% 50 mL if BG < 100. If BG is persistently < 70 after D50% x 2, contact prescriber		• Restart insulin infusion at 50% of previous rate • Round down to the nearest 0.5 units/h		

Fig. 2 Guidelines for titration of insulin infusion in the surgical intensive care unit

Note: Ongoing orders for scheduled mealtime insulin and long-acting insulin will need to be reassessed after the first 24 h.

Glycemic control in the perioperative period Br J Anesthesia 2013

Medical Surgical Units

With regard to treatment of diabetes on med/surg floors, it would appear, on reviewing the literature, that there are many protocols and methods for achieving inpatient diabetic control as there are hospitals. But there are generally agreed-upon principles. It has been shown that using the "sliding scale"-only method doesn't work as well as scheduled insulin dosing with a basal, nutritional, and corrective component (RABBIT studies). Sliding scale alone yields a seesaw-type pattern in glycemic control. Premixed (70/30) preparations can be used twice daily but are also more likely to cause hypoglycemia and lack flexibility. To some degree, they also depend more on timely administration by nursing staff. A basal (detemir or glargine) and nutritional (preferably rapid-acting analogue) plan is best along with corrective dosing. Weight-based dosing seems to be the preferred method (use ADA Clinical Guidelines for this reference).

Below are guidelines useful for controlling patients who have started eating and may be waiting for surgery:

Guidelines for Insulin Use in the Hospital

The following guidelines are an example that can be used in patients who are reasonably stable and eating. They can be available either attached to an

Table 5 Concepts for transition from i.v. insulin therapy to subcutaneous insulin regimen. *ICU* intensive care unit, *BG* blood glucose, *DM* diabetes mellitus, *ADA* American Diabetes Association, *TDD* total daily use

	Donaldson and colleagues[117]	Furnary and Braithwaite[116]	O'Malley and colleagues[115]	Ramos and colleagues[118]	Avanzini and colleagues[120]	Magaji and colleagues[141]
General requirements Indications for transition	Extubated, off vasopressors, intra-aortic balloon pump out, stable renal function, no edema					
	Cardiac surgery Many patients require perioperative insulin infusion Many patients ready to transition on post-op day 1, tolerance of oral intake not essential Major surgery Most patients little need for mealtime bolus I first post-op days Nondiabetics with insulin infusion > 0.5 units h^{-1}	Taking liquids/ regular meals Diabetic diet DM type 2 or hospitalization-related hyperglycemia Receiving < 2 units h^{-1} insulin infusion with BG <7.2 mM (130 mg dl^{-1}) Basal insulin dose <48 units h^{-1} during insulin infusion	DM type 2 on insulin as outpatient DM type 2 with recent mean insulin infusion rate of >0.5 units h^{-1} Stress hyperglycemia or previously unrecognized DM if insulin infusion rate > 1 units h^{-1} or HbA1C above normal Some institutions exclude all stress hyperglycemia patients	Patients on medications for diabetes HbA1c >6% Patients with equivalent of > 60 mg of prednisone and insulin infusion rate >1 units h^{-1} Patients with stress hyperglycemia regardless of insulin infusion rate: no transition to basal subcutaneous insulin	Mean dose of insulin infusion in 24 h before transitions < 1.6 units h^{-1} BG coefficient of variation in 24 h before transition < 11.9%	Patients eating reliably
Calculation of daily insulin dose	Last stable insulin infusion rate × 24 = 24 h insulin dose	Average insulin infusion rate in 6–8 h interval while being NPO and receiving no i.v. dextrose: 6 h total dose × 4 or 8 h total dose × 3	TDD of insulin for 24 h full nutrition: (1) Mena insulin infusion rate per hour from last 6 to 8 h (2) Hourly rate × 24, then multiply by 0.7 or 0.8 = safety-adjusted insulin dose	TDD = averaging hourly drip rate over prior 6 h multiplied By 20 if taking full nutrition (>50% of calories) By 40 if taking minimal nutrition (NPO, <50% of calories)	Estimate of combined basal and nutritional subcutaneous insulin requirements Average insulin infusion rate in last 12 h = mean hourly rate → multiplied by 24 = daily insulin requirement	Patient's hourly insulin infusion rate while NPO × 24 = 24 h basal insulin dose during stress
Basal insulin	80% of 24 h insulin dose = first dose of glargine	Initial glargine dose = 80% of the 24 h basal insulin requirement	Glargine or detemir-40-50% of TDD	50% of TDD = first dose of glargine	Halve daily insulin requirement = basal insulin dose	Adjusted basal dose accounting for stress reduction = 2/3 × 24 h basal insulin dose during stress = units of glargine

(*continued*)

Table 5 (continued)

	Donaldson and colleagues[117]	Furnary and Braithwaite[116]	O'Malley and colleagues[115]	Ramos and colleagues[118]	Avanzini and colleagues[120]	Magaji and colleagues[141]
Bolus (mealtime) insulin	Postprandial BG >7.8 mmol liter^{-1}(140 mg dl^{-1}): add 25% of daily dose of glargine as rapid-acting insulin with each meal	Initiation with first dietary trays, even if insulin infusion still running	Remainder of the TDD = scheduled nutritional insulin. Estimation of first dose: 50% of the TDD as nutritional coverage, divided by 3 to determine mealtime bolus (hold if <50% of meal is eaten) More conservative: 10–20% of basal dose for every meal	50% of TDD divided into regular insulin every 6 h for patients on tube feeds OR lispro (Humalog) before meals if tolerating oral diet	Halve daily insulin requirement and split into: 20% at breakfast 40% at lunch 40% at dinner	Provide as soon patients start eating Depend on patients' caloric intake Start with 10% of adjusted basal dose, given at each meal
Conversion protocol	Overlap first glargine dose with insulin infusion by several hours	Stop insulin infusion 2 h after first glargine dose	Basal insulin at least 2 h before insulin infusion stopped Shorter lead time (30 min) possible if rapid-acting insulin is given with basal insulin	Basal insulin administration of 2 h before insulin infusion stopped	Give first basal insulin dose 2 h before first meal and discontinuation of insulin infusion and i.v. dextrose	Continue insulin infusion at least 4 h after first glargine dose Stop insulin infusion sooner when glargine and rapid-acting mealtime bolus are given
Monitoring BG measurements	Adapt glargine every 24 h Patients without previous DM and normal HbA1c: taper glargine by 20% of first dose per day and discharge without prescription Patients with previous DM: maintain on glargine and mealtime insulin until discharge (transition glargine to previous outpatient therapy modified as required by HbA1c)	BG measurement at: preprandially 2 h postprandially bedtime 3.00 am Revise total 24 h dose daily Revise distribution of basal and prandial insulin daily to approach 50% basal and 50% of prandial	Use carbohydrate counting to cover nutritional intake			Increase mealtime boluses daily according to caloric intake

Transitioning from an insulin infusion to subcutaneous insulin
Adapted with permission from Sebranek JJ et al. British Journal of Anesthesia 2013; Dec 1

inpatient diabetes order set or carried about as a laminated card:

1. Definitions.
   (a) *Basal insulin*: This insulin is the long-acting insulin required to maintain blood glucose levels within a normal range when the patient is not eating. It may be NPH, detemir (Levemir), or glargine (Lantus). *Do not hold insulin if patient is NPO.*
   (b) *Prandial (nutritional/mealtime) insulin*: This insulin is the rapid-acting or fast-acting insulin that is given to cover food intake, TPN, enteral tube feedings, intravenous dextrose, and nutritional supplements. If lispro (Humalog)* is given, it can be given with meals or up to 15 min after the meal.
   (c) *Corrective (supplemental) insulin*: This is the rapid-acting or fast-acting insulin that is given as a *supplement* to the scheduled prandial insulin used to correct hyperglycemia before meals or before bed. Corrective doses should be used with a basal insulin if the patient is eating. It should also be added to any prandial doses that are ordered (i.e., if 10 units are ordered with each meal and the corrective dose algorithm states that the patient should be given 2 units for a blood glucose of 183 at lunchtime, then the lunchtime dose would be 12 units). A bedtime corrective dose is often administered in a smaller dose than other times of the day to avoid nocturnal hypoglycemia. A small snack should also be given with any bedtime dose (i.e., 8 oz of milk and crackers).
2. *Initial* dosing guidelines.
   (a) For *insulin-sensitive patients* (thin with a BMI <20, elderly, on hemodialysis, malnourished, malignancy, or history of prior hypoglycemia)
      - If *eating or receiving bolus tube feeds*
        - Basal insulin 0.1units/kg or 0.2U/kg
        - Prandial insulin 0.05 units/kg with each meal
        - Low- or medium-dose correction algorithm
      - If *NPO* use basal/correction doses as described above and eliminate prandial insulin *only*
   (b) For *average patients* (patients who are an average weight with a BMI of 25–30, no history of hypoglycemia)
      - If *eating or receiving bolus tube feeds*
        - Basal insulin 0.2 units/kg or 0.3U/kg
        - Prandial insulin 0.1 units/kg with each meal
        - Medium- or high-dose correction algorithm
      - If *NPO* use basal/correction doses as described above and eliminate prandial insulin *only*
   (c) For *insulin-resistant patients* (overweight patients with a BMI >30)
      - If *eating or receiving bolus tube feeds*
        - Basal 0.4 units/kg or 0.6U/kg
        - Prandial 0.15units/kg with each meal
        - High-dose correction algorithm
      - If *NPO* use basal/correction doses as described above and eliminate prandial insulin *only*
   (d) For *highly insulin-resistant patients* (obese patients with a BMI > 30), pts on steroids, medications causing hyperglycemia such as nicotinic acid, cyclosporine, and catecholamines or certain antipsychotics such as clozapine or olanzapine
      - If *eating or receiving bolus tube feeds*
        - Basal 0.6units/kg
        - Prandial 0.2 units/kg with each meal
        - High-dose correction algorithm
      - If *NPO* use basal/correction doses as described above and eliminate prandial insulin *only*
3. If the patient was *on insulin prior to this hospitalization and they had good control (as evidenced by the HbA1C)*, then prescribe the same dosages and titrate as described below in titration guidelines.
4. *Titration* guidelines.
   (a) For patients who are *eating or receiving bolus tube feedings.*

   If fasting, premeal and hs blood glucose is 180 mg/dl or greater after 24 h: increase

total daily dose (basal and prandial doses) by 10–20% (1/2 basal and ½ prandial).

If blood glucoses are consistently greater than 180 mg/dl, you may need to increase the total daily dose (prandial and basal) by 20–30% (1/2 basal and ½ prandial).

(b) For patients who are *NPO*

If morning fasting blood glucose is 180 mg/dl or greater after 24 h, increase the basal dose by 10%.

If the other blood glucoses are 180 mg/dl or greater after 24 h, proceed to the next higher-corrective dose algorithm.

(c) If the patient becomes *hypoglycemic fasting (below 70 mg/dl)*, decrease basal insulin by 10–20%.

If the patient becomes *hypoglycemic 2–3 h after a meal (below 70 mg/dl)*, decrease the prandial dose by 10–20%.

5. For transitioning a patient who was on an *insulin infusion*, please see Insulin Infusion Transition Protocol.
6. Special situations.
   (a) *Preoperative and perioperative patients*: Basal insulin is essential during these periods for nearly all patients who have an acute illness. Prandial insulin may not be needed, but they may need corrective dosing. If NPO status is prolonged, an insulin infusion is preferred. See section for NPO patients.
   (b) *Patients with TPN*: A diabetes/endocrine consult is recommended.
   (c) *Patients on insulin pumps from home*: If the physician prescribing the pump is unfamiliar with pump use, a diabetes/endocrine consult is recommended. Please see additional guidelines in the nursing protocol.
   (d) *Type 1 DM*: If the physician treating the patient is unfamiliar with the management of type 1 DM, a diabetes/endocrine consult is recommended.
   (e) *Patients with continuous enteral tube feedings*:
   - *Total daily dose (TDD)*: Give 1 unit of insulin for every 5–10 g of carbohydrate (1:10 g for thinner pts and 1:5 g for more obese patients).
   - *Basal*: Glargine or detemir once daily or NPH twice a day (detemir may also be given twice a day).
   - *Prandial*: Lispro or regular insulin may be used every 4–6 h with or without a basal insulin. Regular insulin may be more effective in this particular setting.
   - *Correction:* Lispro or regular insulin every 4–6 h. Again regular insulin may be more effective because of its longer duration of action.

   *If the tube feeding is stopped for longer than an hour and the insulin was given, you will need to start D10W at 5–10 g/h (see Hypoglycemia Protocol).

   (f) *Patients on steroids:* A single dose of prednisone can last up to 10 h. If the prednisone is given in the morning, then a single dose of NPH with it and corrective doses of aspart with lunch and supper usually work well. For the more potent steroids (dexamethasone, methylprednisolone) in high doses (q. 6 h, q. 8 h), you can easily double the usual doses of insulin (i.e., give 0.4 units/kg as basal and an equal amount in divided doses as prandial with a high-dose corrective algorithm).
   (g) Renal transplantation: It is well known that diabetes will influence the risk of graft failure in renal transplantation. The best time to intervene is before the surgery is carried out, but aggressive control of glucose is warranted in the hospital setting (Therapy for diabetes mellitus and related disorders. 6th edn. . .; 2009; 2015; Taber et al. 2013; Cosio et al. 2008). Steroid-free regimens obviously render the control of blood glucose easier.
   (h) Gastric bypass surgery.
7. Oral medications.
   (a) All of the current oral agents have significant limitations for inpatient use. They also provide little flexibility and are difficult to adequately titrate in the acute care setting. Insulin when used properly can be a more effective tool.

(b) Oral medication advice
- Pioglitazone (Actos) should be avoided with heart failure or liver disease.
- Metformin is contraindicated in patients with renal disease, a creatinine of 1.5 mg/dl in males and 1.4 mg/dl in females, with hepatic disease, with sepsis, and with congestive heart failure requiring medication. It should also be avoided if there is a metabolic acidosis. It should be used cautiously in any ill hospitalized patient. If intravenous contrast dye is to be given, the patient's renal function should be assessed and the medication should be held the day of the procedure if possible. Metformin should not be given for 48 h after the administration of the dye and can be restarted when kidney function has been reevaluated and found to be within normal limits.
- Lispro (Humalog), aspart (Novolog), or glulisine (Apidra) have nearly identical action and may be used interchangeably.

Special Situations

Renal transplantation: It is well known that diabetes will influence the risk of graft failure in renal transplantation. The best time to intervene is before the surgery is carried out, but aggressive control of glucose is warranted in the hospital setting (Valderhaug et al. 2012; Jacobi et al. 2012). Steroid-free regimens obviously render the control of blood glucose easier.

Gastric bypass surgery: The type 1 patient undergoing bariatric surgery will require continual provision of insulin; management by a specialist is strongly recommended. Weight-based dosing in the type 2 diabetic may mislead in this situation. In the short duration type 2 diabetic "sliding scale" may be adequate. If the patient was on insulin doses prior to surgery, frequent glucose testing should be done and prior doses reduced by 50% along with provision of dextrose in IVF while in the hospital.

Conclusion

All surgeons, general or subspecialty, will see patients with diabetes in their practice in view of the high prevalence of diabetes. Control of the blood glucose matters a great deal with respect to outcomes and for optimal utilization of resources. Consensus has been reached regarding goals for glucose control. Many organizations, surgical and medical, have published recommendations and guidelines for the care of diabetic inpatients. The use of order sets and guidelines for in-hospital care can greatly facilitate care for these patients. Insulin is the preferred way to control blood glucose. For critically ill patients, an insulin infusion is the best way to ensure good control. Guidelines exist for the transition from an infusion to subcutaneous insulin. A knowledge of oral medications is useful both in preoperative evaluation and upon discharge. Special situations require different management strategies.

Cross-References

▶ Medical Evaluation of the Diabetic Patient for Pancreas Transplant

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UNOS Perspective on Pancreas Transplantation

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Contents

Abstract

The Organ procurement and Transplantation Network (OPTN) develops pancreas transplant allocation policy under Federal Government contract from the Health Resources and Services Administration (HRSA). This system was established when Congress passed the National Organ Transplantation Act (NOTA) in 1984. OPTN data are collected by the United Network for Organ Sharing (UNOS) for outcomes analysis and transplant program oversight. Despite improving clinical results, the number of pancreas transplants done in the United States has seen a significant decline over the past 10 years. There have also been declines in the number of additions to the pancreas transplant waiting list. This may be in part related to changes in the medical management of diabetes and changes in the organ donor population. In 2014 a new OPTN pancreas allocation system was instituted. Prior to this pancreas allocation varied with respect to how pancreas allocation integrated with kidney allocation. A uniform definition of pancreas allograft failure has also been developed which will be used to report pancreas graft and patient outcome by the Scientific Registry of Transplant Recipients (SRTR). The OPTN continues to work to devise policy strategies with a goal to remove structural barriers to pancreas transplantation and improve data collection.

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Pancreas allocation · United Network for Organ Sharing · Allocation policy · Pancreas transplant outcomes · Policy development · Organ Procurement and Transplantation Network (OPTN) · Pancreas kidney transplantation · Solitary pancreas transplantation

Introduction

The Organ Procurement and Transplantation Network (OPTN) has been responsible for developing pancreas transplant allocation policy since its inception in 1986. This system was established when Congress passed the National Organ Transplantation Act (NOTA) in 1984 (https://www.organdonor.gov/about-dot/laws/history.html). Until the early 1970s individual transplant hospitals and organ procurement organizations managed all aspects of organ recovery and transplantation. Organs not transplanted at hospitals near the donor hospital often were wasted. Regional organ sharing consortia using computerized databases came into use in the later 1970s but there was no requirement for transplant centers to share organs prior to the passage of NOTA. The increasing clinical success of organ transplantation resulted in higher demand for transplantation by patients in need of organ replacement. This revealed the inefficiencies of the organ sharing system and a critical shortage of donor organs. NOTA set up the guidelines to establish the OPTN and maintain a national computer registry for matching donated organs with appropriate recipients. The OPTN was also tasked with collecting and analyzing clinical data about organ donors, transplant candidates, and transplant recipients.

NOTA called for the OPTN to be operated by a private, nonprofit organization under federal contract. The United Network for Organ Sharing (UNOS), which evolved from a regional organ sharing consortium, secured the initial contract from the Department of Health and Human Services (HHS) to operate and further develop the OPTN. UNOS has remained the OPTN contractor since 1986. Operational rules issued by HHS, the OPTN Final Rule, finalized in 2000 guide allocation policy development by the OPTN, as well as performance oversight of transplant programs and Organ Procurement Organizations (OPOs) (https://www.gpo.gov/fdsys/pkg/FR-1998-04-02/pdf/98-8191.pdf). This includes setting patient listing requirements and polices which rank order potential recipients based on the characteristics of each donor organ. Under NOTA and its operational guidelines organ allocation policy must meet a number of legal requirements. Policy must be based on sound medical judgment, be designed to avoid wasting organs, and be able to achieve equitable allocation of organs. Notably, policy is not to be based on a candidate's place of residence or place of listing. The operational rules require the use of standardized minimum listing criteria and priority ranking using objective and measurable medical criteria to the extent possible, to distribute organs over as broad a geographic area as feasible, and to apply appropriate performance indicators to assess transplant program performance. These policies are required to be periodically reviewed and revised as needed. Regulations also require giving patients, families, and physicians accurate and timely information to assess the performance of transplant programs including risk-adjusted patient and graft survival rates following transplantation, risk-adjusted waiting time, and risk-adjusted transplantation rates. These metrics are also used for program oversight by the OPTN and the Center for Medicare and Medicaid Services (CMS) (https://www.cms.gov/Medicare/Provider-Enrollment-and-Certification/GuidanceforLawsAndRegulations/Transplant-Laws-and-Regulations.html, Final rule. Fed Regist. 2007 72:15197–280).

The OPTN develops allocation policy through a relatively structured process that includes input from the public as well as patients and the transplant community (https://www.unos.org/policy/policy-development/). Typically allocation policy proposals originate with an organ-specific OPTN committee. OPTN committees have representation from all of the 11 OPTN geographic regions, from the general public, and often transplant recipients, organ donors, or organ donor families. At a high level, the development of a modification to an allocation policy proceeds in the following

steps. An OPTN committee demonstrates, using evidence-based analytics, the etiology and operational characteristics of a problematic issue with current allocation policy existing within the transplant system. It is the intent that allocation policy will evolve as clinical transplantation changes, and new approaches or results suggest the need for changes to address organ allocation equity or to improve outcomes or system efficiency. The committee initiates discussion of the problem and possible solutions, collaborating with interested stakeholders and other OPTN committees. The committee must seek approval from the OPTN Policy Oversight and Executive Committees for approval to use OPTN resources to address the problem and to assure that committee efforts align with OPTN strategic goals. During the development process there is extensive predictive modeling of the expected outcomes of any proposed allocation system changes to provide assurance that the changes will meet goals set out by the Committee. This modeling is done in conjunction with the Scientific Registry of Transplant Recipients (SRTR), a separate HRSA contractor charged with support of the OPTN using OPTN data as well as additional data sources. A finalized proposal is presented at all regional meetings for feedback and is also distributed for open public comment. The OPTN policy development process incorporates feedback on policy and bylaws proposals, before the proposals go to the OPTN board of directors for approval. Public comment is an essential part of the policy development process. All interested individuals are welcome to participate, especially transplant candidates, who are most affected by policies. To encourage public participation and promote transparency, submitted comments are published online. Once the public comment period closes, the committee reviews all the comments, and in collaboration with interested stakeholders, makes a final recommendation to the OPTN Board of Directors. If approved by the Board of Directors, the system changes are programed by the UNOS Information Technology Departments. Depending on the complexity of the changes UNOS provides substantial educational resources for the transplant community to prepare for the revision of the allocation system. This policy development process has the benefit of transparency but can require up to two years or more to complete.

Trends in Pancreas Transplantation

The outcomes of pancreas transplantation as measures by patient survival and graft survival, both short term and longer term, have improved over time (Redfield et al. 2016, http://srtr.transplant.hrsa.gov/annual_reports/2012/Default.aspx). Despite these improvements, the number of pancreas transplants done in the United States has seen a significant decline from 2005 through 2015. This is true for simultaneous kidney pancreas transplants (SPK), pancreas after previous kidney transplants (PAK), and pancreas transplants alone (PTA). This trend is most notable in isolated pancreas transplantation that is PAK and PTA transplants, but is also significant in SPK transplantation. Data from the OPTN database shows that in 2015 there were 719 SPK transplants performed in the United States. This same year 226 isolated pancreas transplants were done representing 79 PAK and 147 PTA transplants. As can be seen in Fig. 1, these numbers represent a gradual and sustained decrease in pancreas transplant numbers. In 2005 there were 903 SPK transplants and 540 isolated pancreas transplants with 336 PAK transplants and 204 PTA transplants. These numbers demonstrate that over the past 10 years there has been a striking 34% decrease in total pancreas transplant numbers and a 20% decline in SPK transplants. Most dramatic has been the decrease in PAK transplantation which fell by 76% with PTA transplants decreasing by 28%. The peak number of pancreas transplants in the United States was in 2004 when 1475 total transplants were done (data from OPTN database).

The decline in the numbers of pancreas transplants in the United States over the 10 year time frame is also mirrored by steep declines in the number of additions to the pancreas transplant waiting list. In 2015 there were 1264 new recipient registrations for SPK transplantation and

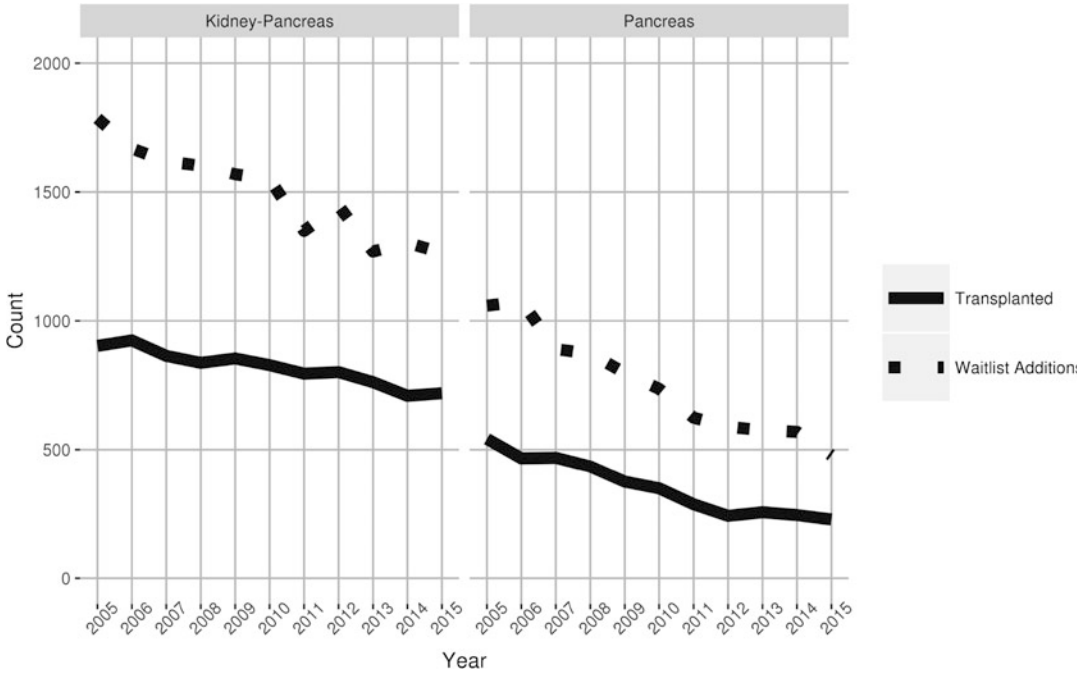

Fig. 1 The number of waitlist additions and transplants by year and organ type. Both the waitlist and transplant volumes have been decreasing over time

478 for isolated pancreas transplantation (Fig. 1). Ten years previously in 2005, the demand for pancreas transplantation, measured by new wait list registrations, was substantially higher with 1786 total new SPK registrations (Fig. 1) and 1059 new pancreas registrations. The magnitude of the decrease in new patients registering for pancreas transplantation (38%) is very similar to the magnitude of the decrease in the numbers of pancreas transplants currently being performed. This suggests that falling demand for pancreas transplantation, as estimated by new waitlist additions, may be responsible for the national decline in pancreas transplantation clearly evident in the United States over the past 10 years although multiple other contributing factors have been discussed in the literature (Stratta et al 2016a, 2016b; Niederhaus 2015).

One possible factor contributing the declining pancreas transplant numbers has been the clinical improvements in the medical management of diabetes. This has included the introduction of multiple new insulins that increase the flexibility of clinical use and provide improved glucose control with less hypoglycemia. There have also been new classes of medications introduced that have dramatically increased therapeutic options for type 2 diabetes. Perhaps equally important has been the introduction of technologies for the administration of insulins and increasingly sophisticated glucose real-time glucose monitoring. The combination of these two technologies has resulted in the introduction of closed loop systems with insulin administration controlled by a glucose sensor without direct patient input. These approaches have decreased the incidence of secondary complications of diabetes such as severe autonomic neuropathy and perhaps decreased the population of patients with labile brittle diabetes that have been candidates for pancreas transplantation.

Other factors potentially contributing to the decline in pancreas transplantation have been shifts in the deceased donor population affecting donor pancreas quality (Stratta et al. 2016b; Fridell et al. 2010). Increasingly deceased donors with a nontraumatic cause of brain death have become relatively more obese and older resulting

Table 1 Total number of donors, defined as having at least one organ recovered for transplantation, the number of donors who were also pancreas donors, and the number of pancreata procured but not transplanted in two 18-month time periods beginning in 2005 and 2013

	2005	2013
Total number of donors	11619	12702
Number of pancreas donors	3089	1994
Number of pancreata discarded	875	467

in a decline in the percentage of donors appropriate for pancreas procurement. Analysis of OPTN data, shown in Table 1, finds that during an 18-month period beginning in 2005, 26.6% of deceased donors were pancreas donors resulting in the procurement of 3089 pancreata. Of these procured 3089 organs, 28.3% were not transplanted. During a similar time period starting in 2013 the percentage of deceased donors that were also pancreas donors dropped by almost half to only 15.7% yielding 1994 organs. The percentage that were not transplanted was slightly lower at 24.4%. It has been speculated that with shorter waiting lists transplant surgeons have become more selective in the organs that are transplanted (Pondrom 2015).

The decline in pancreas transplantation in the United States is especially notable given the expanded indications for pancreas transplantation which now in many pancreas transplant programs include type 2 diabetes (Redfield et al. 2015). Pancreas transplantation was initially offered only to candidates with type 1 diabetes. The introduction of newer immunosuppressant medications in the 1990s resulted in a significant improvement in pancreas transplant outcomes and growth in the number of patients seeking pancreas transplantation. This also generated interest in considering whether pancreas transplantation could be effective treatment in patients with type 2 diabetes as well as type 1 diabetes. Given the much larger numbers of patients with type 2 diabetes compared to type 1 diabetes this had important implications for pancreas transplantation. Defining appropriate patients with type 2 diabetes who might benefit from pancreas transplantation was a challenge.

Unlike type 1 diabetic pancreas transplant recipients, the number of patients with type 2 diabetes receiving pancreas transplants has actually increased over the past 10 years, although these numbers still remain relatively small. In 2005 there were 47 patients with type 2 diabetes transplanted as 34 SPK transplants and 13 isolated pancreas transplants. In 2015 there were 98 pancreas transplants in type 2 patients comprised as 87 SPK transplants and 11 pancreas alone transplants. In the 2015 data, new SPK registrations for type 2 diabetic patients stayed relatively flat; in 2005 there were 155 new type 2 candidate registrations for SPK transplant and 152 in 2015. In 2005, there were 57 patients with type 2 diabetes registering for isolated pancreas transplantation, and in 2015, 24 type 2 diabetics registered for isolated pancreas transplantation. Although the number of type 2 diabetic patients receiving SPK transplants has gradually increased, the number of type 2 diabetic patients receiving isolated pancreas transplants remains very limited with 13 such transplants in 2005 and 11 in 2015. Although increasing, the use of pancreas transplantation for type 2 diabetes remains limited and how it will evolve in the future is not clear.

There are currently 131 approved pancreas transplant programs in 2016 in the United States. This is a small decrease from the 141 approved pancreas transplant programs in 2005. Of these centers 117 actually performed a pancreas transplant either as an SPK or an isolated pancreas transplant. A total of 14 centers (11%) did not perform a transplant, and 19 centers (15%) performed only 1 transplant. Most pancreas transplant centers actively provide SPK transplantation but fewer are providing isolated pancreas transplantation in the form of PAK or PTA transplants. In 2015, 110 transplant programs performed at least 1 SPK transplant, 42 performed at least 1 PAK, and 37 performed at least 1 PTA. A similar number of centers did SPK and PTA transplants in 2005. There were, however, 83 transplant centers doing PAK transplants in 2005. These data demonstrate that most pancreas transplant programs operate at very low volumes. The medium transplant center volume of SPK transplants per year was 5.0 in 2015. For isolated pancreas

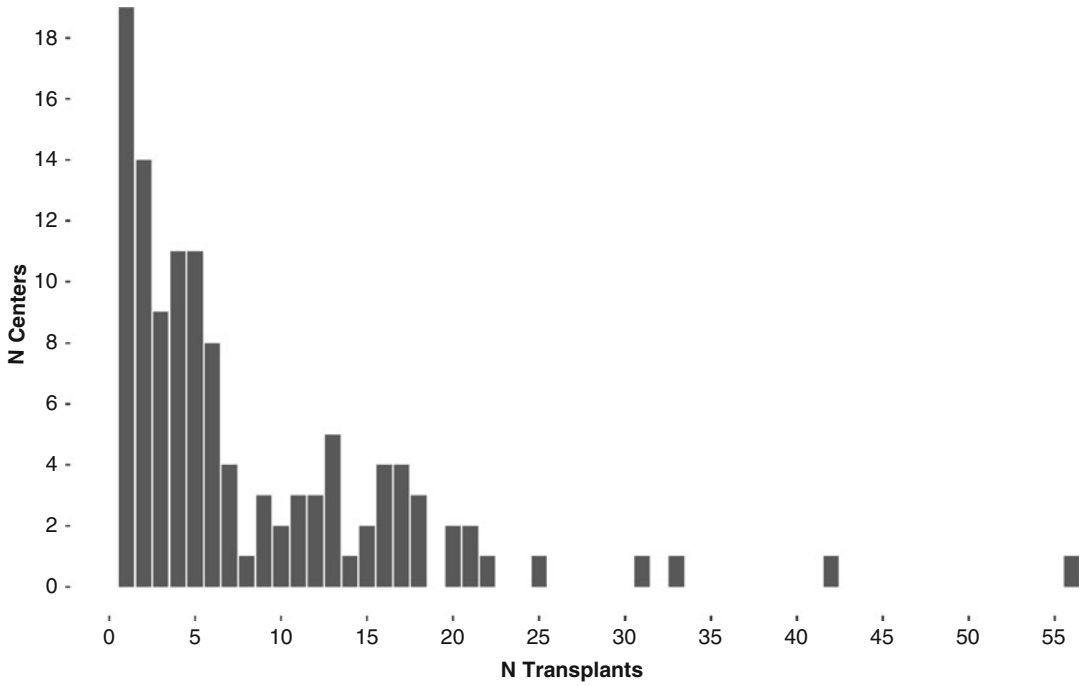

Fig. 2 The number of transplant programs approved to do pancreas transplants in 2016 and the distribution of the number of pancreas transplants performed. There are 131 programs approved to do pancreas transplants, of these 117 performed a pancreas or kidney pancreas transplant from 7/1/2015 to 6/30/2016

transplantation the median annual transplant volumes were 2.0 for both PAK and for PTA transplants. It is of interest that in the current setting of declining pancreas transplant volumes these median center volumes by pancreas transplant type are unchanged from 2005. Figure 2 shows the distribution of the number of transplants performed by center which demonstrates that there are only 10 pancreas transplant programs that do 20 or more pancreas transplants on an annual basis.

With most pancreas transplant programs operating at very low annual transplant volumes there arise legitimate concerns regarding adequacy of training opportunities and maintenance of clinical currency. From an OPTN regulatory perspective the issue of program functional inactivity for pancreas transplant programs is an ongoing concern since many programs are on the borderline. Programs that meet the OPTN policy definition for functional inactivity are reviewed by the Membership and Professional Standards Committee. Programs are expected to serve the needs of patients on their waiting list and there are requirements for patient notification if a program is not actively doing pancreas transplants. Current OPTN policy defines functional inactivity for pancreas transplantation as a program that is doing less than 1 transplants over a six month period. In addition to patient notification functionally inactive programs are required to demonstrate how clinical currency of staff is maintained. In OPTN policy functional inactivity is defined differently for each transplanted organ. Pancreas transplant programs are the program type most commonly cited for functional inactivity by the OPTN.

These low pancreas transplant volumes also impact the ability of the system to provide adequate training opportunities for surgical transplant fellows and for transplant medicine fellows. OPTN policy defines training and experience required to meet the criteria to function as a pancreas transplant program Surgical Director or a Medical Director, both being positions required for program approval. Currently, surgical fellows in training are required to be primary or first

assistant on 20 pancreas transplant procedures over two years. Transplant Medicine fellows commonly receive their pancreas transplant training in the context of a one-year transplant nephrology fellowship. Transplant Medicine fellows are required to manage eight new pancreas transplant recipients during this one year of training as part of criteria to serve as a pancreas transplant medical director. It is apparent that in the current environment of declining transplant numbers that opportunities for clinical training in pancreas transplantation are declining. There is concern in the pancreas transplant community that diminished training opportunities are a threat to the ability to maintain adequate manpower to sustain the field. The UNOS Pancreas Transplant Committee has an ongoing initiative studying the factors responsible for the decline in pancreas transplantation and to devise research and educational strategies to address these concerns. A focus is on dissemination of recent data documenting improved clinical outcomes for pancreas transplant recipients. There are also proposals to more effectively engage patients and providers on the evolution of the appropriate role of pancreas transplantation within the various treatment options for both type 1 and type 2 diabetes. The recent adoption by the OPTN of a new pancreas allocation algorithm and revision to the system of facilitated pancreas allocation are designed to increase allocation effectiveness and allow transplant programs to increase pancreas transplant volumes.

The OPTN Allocation System for Pancreas Transplantation

In 2014 the OPTN instituted a new pancreas allocation system (https://www.transplantpro.org/news/kidney/new-pancreas-transplant-policies-take-effect/). The OPTN Pancreas Transplant Committee spent several years developing this national pancreas allocation system to better address the needs of patients with diabetes with and without concurrent renal failure.

Historically, there had never been a uniform national policy for pancreas allocation (Smith et al. 2012). The Pancreas Transplant Committee had a number of concerns with the way pancreata were allocated. The allocation of pancreas allografts depended on how many kidneys were available from the donor at the time of allocation. If two kidneys and a pancreas were available, one kidney would be allocated to candidates on the kidney-alone waiting list. The remaining kidney and pancreas were then allocated to zero HLA-mismatched SPK candidates who were highly sensitized. After these zero HLA-mismatch offers, at the discretion of the Organ Procurement Organization (OPO), the kidney and pancreas could be allocated to other SPK candidates or to solitary pancreas candidates with the kidney offer going back to candidates on the kidney alone list. The OPO could choose any of the three waiting lists and switch among them but no candidates could be skipped on the selected lists. On whatever list was chosen, the OPOs were required to follow allocation sequencing defined in OPTN policy specific to that list. At any point, however, the OPO could choose to switch from the SPK list to the solitary pancreas list and the kidney alone list. As an example some OPOs choose to offer a kidney and pancreas to local SPK candidates first then switch to the solitary pancreas list. The solitary pancreas list sequences were further stratified by donor age and BMI with a separate match for donors greater than 50 years old or with a BMI greater than 30 kg/m^2.

To assess the variability within the pancreas allocation system the OPTN Pancreas Transplant Committee surveyed the 58 OPOs on their allocation practices. OPOs were classified into groups based on three categories: the kidney follows the pancreas; the pancreas follows the kidney; or a mixed approach. Out of the 53 DSAs that allocated the pancreas locally, 43 DSAs were classified as kidney follows the pancreas, 4 as pancreas follows the kidney, and 6 as mixed. Of the DSAs where the kidney followed the pancreas, 28 give SPK absolute priority, 4 give PA absolute priority, and 8 had a combined SPK/PA list based on waiting time.

A consequence of this complicated and variable allocation approach was that waiting time for SPK transplants and pancreas transplants varied

widely across the country in part because of local or regional allocation decisions. Furthermore, this system did not seek to maximize the utilization of the pancreata. SPKs received offers after other renal or extrarenal multiorgan transplants, kidney paybacks, and zero mismatch kidney-alone candidates. This allocation sequencing was felt to lead to discard of pancreas allografts that would likely have been accepted if offered in the context of SPK transplantation but were declined for solitary pancreas transplants. Under the previous system, 66% of pancreata were used for SPK transplant candidates. Under the previous allocation system there were no specific listing criteria for SPK transplants with respect to the nature of pancreas dysfunction necessary to qualify to receive waiting time for an SPK transplant.

New Pancreas Allocation System

With the recognition that the existing pancreas allocation system, the result of a gradual evolution of OPTN policy dating back to 1986, was not optimally meeting the needs of patients, transplant programs, or OPOs, OPTN undertook a major revision of pancreas allocation policies. The goals of the revised system as set out by the Pancreas Transplant Committee were to establish a uniform, national system to govern how pancreas allografts were allocated. It was intended that this allocation system would address multiple issues including reduction in geographic inequities of access and waiting time. It was hoped that the changes would reduce barriers limiting transplant programs' ability to increase utilization of the pancreas allografts and to maximize the capacity of the OPTN allowing more pancreas transplant candidates to have an opportunity for transplantation. It attempted to standardize the pancreas allocation process and increase access to organs reducing waiting times for both SPK and solitary pancreas candidates without significantly adversely affecting access and waiting times for pediatric and adult kidney alone recipients. The intent was to also minimize impact on kidney alone recipients based on ethnicity, age, and gender. An important component of the new allocation system was the development of appropriate qualifying criteria for candidates waiting for an SPK transplant. Overall the new allocation system for pancreas transplantation was intended to enhance operational efficiency, reduce computer programming requirements, and decrease OPO and OPTN administrative costs for pancreas allocation by disentangling it from the kidney allocation system. By disentangling pancreas allocation from kidney allocation, SPK candidates would no longer be subject to disparities that resulted variable allocation practices in the DSA.

The new system, instituted in 2014, incorporated extensive feedback from public comment and multiple stakeholders. Because the clinical outcomes for PTA and PAK transplants had steadily improved and were approaching the pancreas allograft outcomes of SPK recipients it was felt that the SPK and solitary pancreas waiting lists should be combined. A single list for all pancreas candidates would eliminate complexities in pancreas allocation. This would provide candidates for all types of pancreas transplants with an equal opportunity for high quality pancreata and remove potential disincentives for the use of living donors by appropriate candidates for PAK transplantation. It also would retain additional high quality kidneys within the kidney allocation system in cases in which the pancreas is used for solitary transplantation which was a major concern of the kidney transplant community. This approach was also consistent with the allocation of kidney allografts with other extra-renal organs.

The system includes objective medical qualifying criteria for kidney function and glucose intolerance in order for patients to accrue waiting time. To qualify for an SPK transplant the patient was required to meet the criteria for accrual of waiting time under kidney transplant allocation policy. Kidney transplant policy requires that to accrue waiting time the patient be on dialysis or have a glomerular filtration rate or creatinine clearance less than or equal to 20 mL/min. Accrual of waiting time for an SPK transplant was also restricted to patients with diabetes mellitus who were on insulin and had a c-peptide less than or equal to 2 ng/mL. Patients on insulin with a c-peptide greater than 2 ng/mL were

required to have a BMI of less than or equal to 30 kg/m^2 to accrue SPK waiting time. The BMI value of 30 kg/m^2 is derived from the standard definition of obesity of a BMI over 30 kg/m^2. These waiting time criteria were expected to limit SPK transplantation for patients not in renal failure as well as for patients who could potentially improve their glucose tolerance by methods other than transplantation. Candidates not meeting criteria for SPK waiting time could still qualify for kidney alone waiting time or pancreas alone waiting time. Waiting time for pancreas alone transplant candidates begins at the date of listing. Pancreas candidates must be diagnosed with diabetes or have pancreatic exocrine insufficiency or require the transplantation of a pancreas for technical reasons as part of a multi-organ transplant.

This new allocation system improved operational effectiveness for OPOs. With the new system OPOs only needed to run a single match run when allocating pancreata, as opposed to three match runs under the previous system. OPO staff no longer had to arbitrate disputes over the kidney between pancreas and kidney programs.

Because of the declining number of pancreas transplants the OPTN revised the previously developed process of facilitated pancreas allocation. This was designed to increase pancreas allograft utilization by preferentially allocating pancreata likely to be difficult to place to a limited group of pancreas transplant centers interested in transplanting organs from outside their DSA and was based on facilitated access to pancreata once local offers were declined. Given the generally low rate of pancreas recovery this expedited allocation was felt to be a prudent approach to increasing pancreas utilization. Participation in facilitated allocation required a written agreement between the transplant program and the OPTN. With the revised facilitated pancreas allocation scheme, organs could be offered if no candidate had accepted a pancreas offer from the OPO or OPTN Organ Center within five hours of the initial offer or if the Organ Center was notified that procurement of the pancreas would occur within one hour. Previous data analysis had shown that the average time from offer acceptance to organ procurement was 19 h. Pancreata not accepted prior to procurement had high rates of discard. While initially successful the number of organs transplanted through facilitated allocation declined to relatively small numbers. In 2012 and 2013 there were only 10 total pancreas transplants performed using facilitated allocation. There were programs with written agreements for facilitated allocation that were not actively using the system. The system of facilitated pancreas allocation was revised in 2016 to require participating programs to have transplanted a minimum of five pancreata from outside its DSA in the previous two years. Facilitated placement then could be used to send offers only to qualified centers once the local list has exhausted on a match run. Additionally the system could be used by both OPOs and the OPTN Organ Center and the time prior to procurement was increased to three hours.

An initial analysis of the performance of the pancreas allocation system over the first six months of operation has shown mixed results and suggests that the system has fallen short of meeting some of its major goals (Carrico and Fridell 2016). There was no significant shift in the proportion of pancreas alone transplants to SPK transplants. Additionally the percent of deceased donors that were pancreas donors, either PA or SPK, did not change. During the six month interval prior to the allocation change there were 4217 deceased donors of which 8.3% were also SPK donors and 2.8% were PA donors. In the first six months under the new allocation system there were 4495 deceased donors of which 8.0% were SPK donors and 2.5% were PA donors (Carrico and Fridell 2016). The risk of pancreas organ discard is known to be related to the Pancreas Donor Risk Index (PDRI) (Axelrod et al. 2010). The difference in odds of pancreas discard before and after the new allocation by PDRI was not significant Ideal pancreas donors defined by PDRI and other clinical characteristics had pancreas organ recovery in 56.9% of cases prior to allocation change and in 58.8% of cases following allocation change which was not statistically significant. This does suggest that significant capacity to increase organ procurement from ideal donors remains in the system. Donors that did not meet the

ideal donor criteria were recovered at a significantly lower rate both before and after allocation change (8.5% vs 7.9%, respectively). There was a marginal increase in the percent of SPK transplants performed regionally compared to locally increasing from 10.4% prior to allocation change to 15.8% after allocation change ($p = 0.06$). These results do not include the effects of the revised facilitated pancreas allocation because sufficient data for analysis has not accumulated. Whether or not the revised facilitated allocation system will increase pancreas utilization will be determined when data becomes available.

Pancreas Transplant Outcomes

One of the major responsibilities of the OPTN is to use the data collected by the OPTN to report organ transplant outcomes. This is required by regulations promulgated in the NOTA legislation. This is done for the purposes of quality oversight of transplant programs and to inform patients and the general public of program specific outcomes. This has been traditionally done by assessing one-year patient and allograft survival. These program specific reports are prepared by the SRTR using data collected by the OPTN. The program outcomes are measured against risk-adjusted program specific expected outcomes using models developed by the SRTR. Defining pancreas graft outcomes has been difficult because of the lack of a nationally agreed upon and consistently utilized definition of how to identify and document pancreas allograft failure. The definition of allograft failure applied to all solid organ transplants has been defined in OPTN policy as occurring when an organ is removed, a recipient dies, or a recipient has been placed on a chronic allograft support system. The reporting of pancreas outcomes has been further complicated by the collection of post-transplant pancreas graft function as "functioning, partial function, of failed." Partial function was described as the patient taking some insulin but less than 50% of the usual amount taken before transplant, or the presence of c-peptide. A failed graft was described as the patient being completely dependent on insulin or oral medication for blood sugar control. A c-peptide threshold was not specified and the definition did not distinguish between type 1 and type 2 diabetes. The limitations of this definition made the graft outcomes of pancreas transplantation difficult to describe. It has been noted that some centers were reporting graft failure upon resumption of any diabetes medications while other centers report graft failure when a recipient resumes diabetic medication at the pre-transplant level. The precise definitions used by a transplant center were not clear and how consistently a definition was used within a transplant program was not clear. With these caveats the SRTR reported program specific pancreas outcomes until 2013 although these reports were not used by the OPTN Membership and Professional Standard Committee for program oversight based on graft outcomes. Since 2012 the SRTR has not reported program specific or national one year pancreas allograft survival.

Because of these limitations the OPTN Pancreas Transplantation Committee worked to develop a consistent definition of pancreas allograft failure that could be used for reporting of graft outcomes. The lack of c-peptide or a lower limit of c-peptide was proposed by some an objective measure of pancreas allograft failure. The Pancreas transplant Committee undertook a survey of pancreas transplant program practice to determine a value of c-peptide that corresponds with pancreas allograft failure. Data from seven centers spanning ten years of outcomes found that there was not a consistent c-peptide threshold that clinicians used to determine when a pancreas had failed. The data suggested that the determination of allograft failure using c-peptide was on a case-by-case basis. C-peptide levels showed large fluctuations and that graft failure was being reported at all levels of c-peptide values. After extensive debate a compromise was reached that the use of 0.5 units/kg/day for 90 consecutive days is indicative of graft failure. This definition was felt to create a starting definition which could be expanded on as additional clinical data becomes available. This definition is being implemented as OPTN policy but has not yet produced sufficient data for the SRTR to use as the basis for program specific reports.

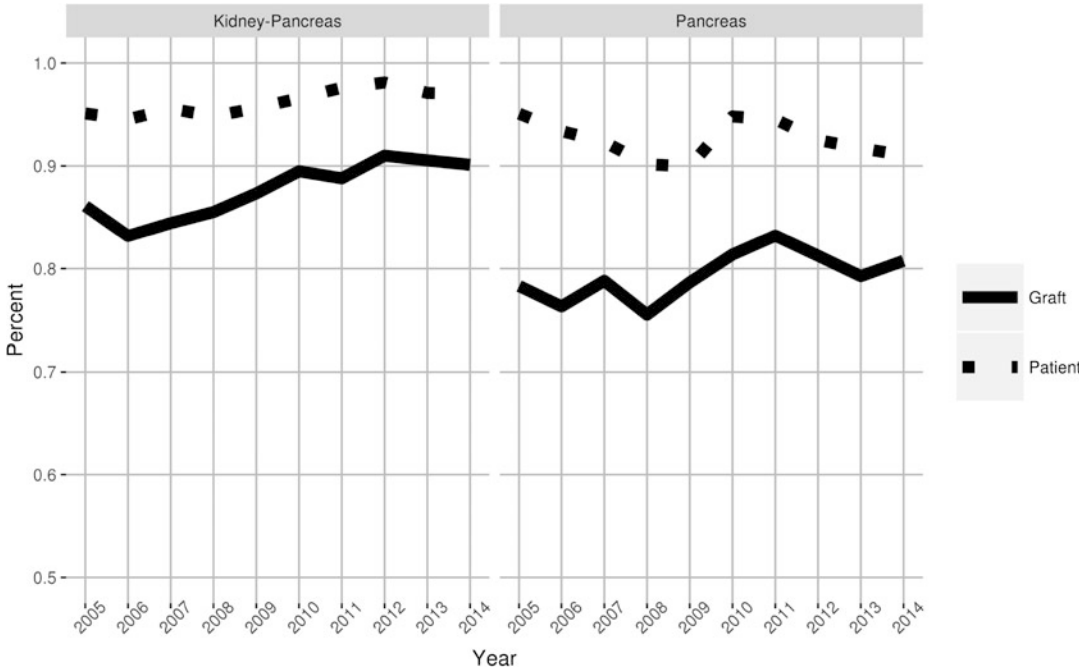

Fig. 3 One-year patient and graft survival from 2005 to 2014 for kidney-pancreas and pancreas transplant recipients

Within the limitations of the current graft survival definition it is still possible to discern trends in patient and reported graft survival, both short term and long term over the past decade of pancreas transplants. Although the new definition is not yet implemented, programs are required to submit follow-up on recipients at specified time frames post-transplant, and graft status is required. Figure 3 shows one-year patient and graft survival for kidney-pancreas and pancreas alone recipients from 2005 through 2014. Data from the OPTN database shows that one-year unadjusted patient survival differs between kidney-pancreas and pancreas alone recipients. In 2014 the one-year patient survival for kidney-pancreas recipients was 97% while the one-year patient survival for pancreas alone recipients was 91% although there is substantial year to year variation likely due to low numbers. Within each patient group there has not been a statistically significant change in the one-year patient survival over the 2005–2014 time period. In 2005 one-year patient survival was 95% for kidney-pancreas recipients and 95% for pancreas alone recipients. Neither of these are statistically different from 2014 data. The data for one-year unadjusted graft survival is similar. The one-year pancreas graft survival for kidney-pancreas recipients rose from 86% in 2005 to 90% in 2014. One-year pancreas graft survival for pancreas alone recipients was 78% in 2005 which increased to 80% in 2014.

Longer-term patient and graft survival are shown in Figs. 4 and 5 and provide the patient and graft survival of transplants done between 2000 and 2005. In the 2005 recipient cohort for kidney pancreas recipients 5 year patient survival was 88% and 10 year patient survival was 75%. The 5 and 10 year patient survival for pancreas alone recipients was 85% and 63% respectively. Pancreas graft survival for kidney-pancreas recipients transplanted in 2005 was 74% at 5 years and 61% at 10 years. Pancreas graft survival for pancreas transplant alone recipients transplanted in 2005 was 55% at 5 years and 41% at 10 years.

The median waiting time to transplant has decreased substantially for kidney-pancreas

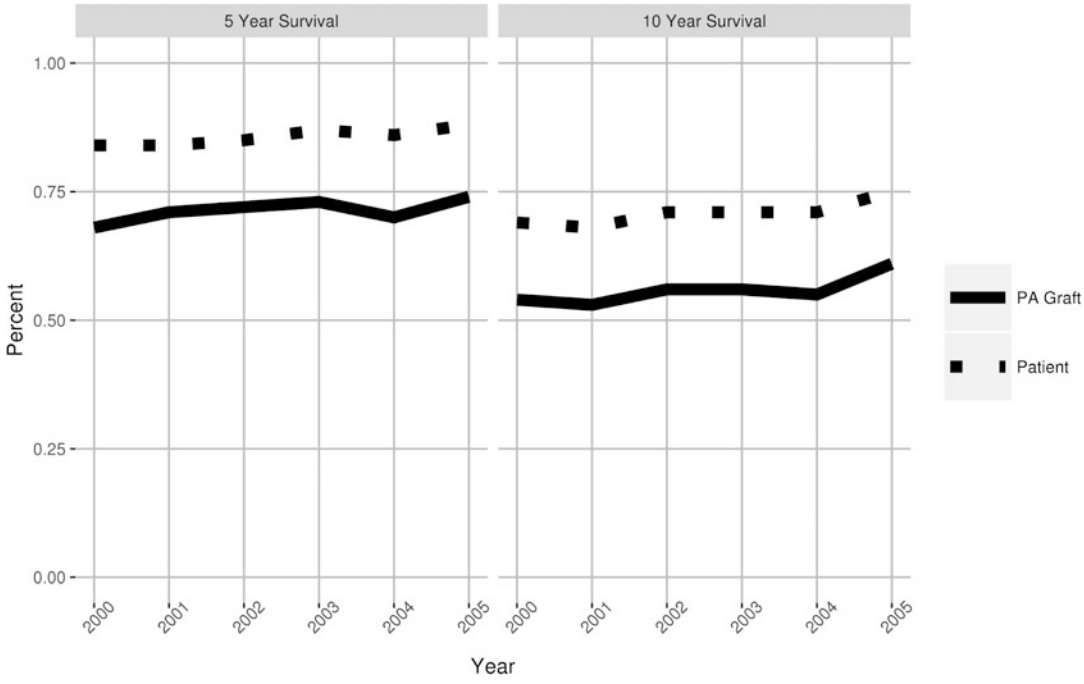

Fig. 4 Five- and 10-year patient and graft survival for kidney-pancreas transplants. The transplants in this analysis took place from 2000 to 2005

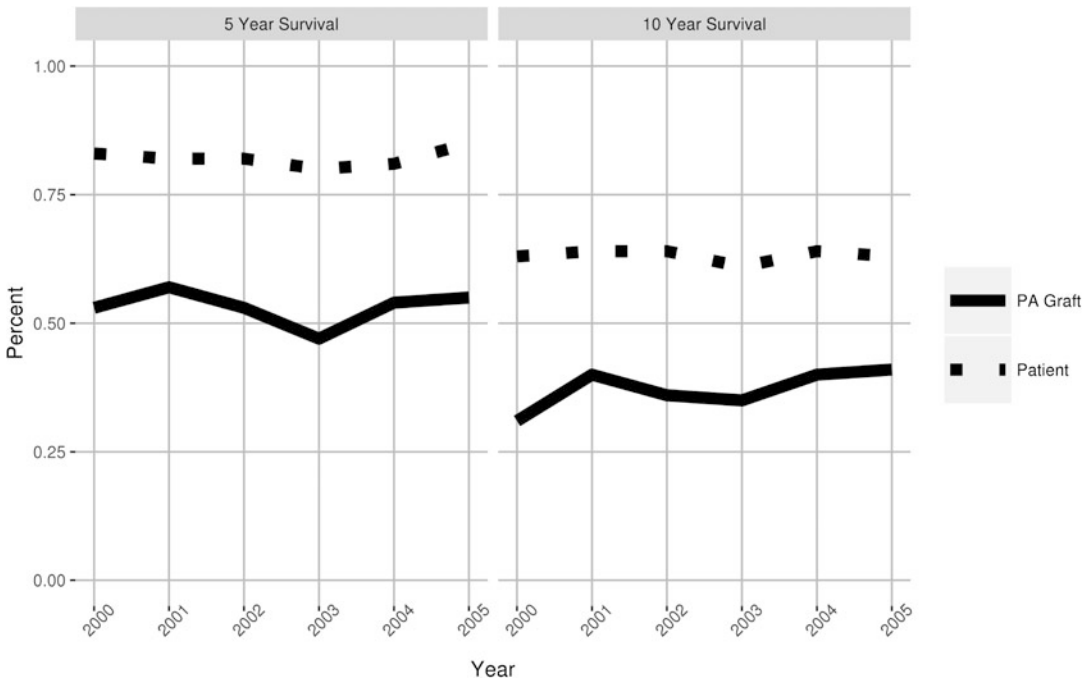

Fig. 5 Five- and 10-year patient and graft survival for pancreas transplants. The transplants in this analysis took place from 2000 to 2005

recipients decreasing from 5.4 years for patients listed in 2005 to 2.4 years for patients listed in 2010. Waiting time for pancreas transplant alone has seen less change. Median waiting time was 1.6 years for patients listed in 2005 and was 1.8 years for patients listed in 2010.

Conclusion

The field of pancreas transplantation continues to evolve in directions different from other solid organ transplants. Transplant volumes for both SPK and pancreas alone transplantation continue to gradually decline. This has been most significantly seen in PAK transplants. Demand for pancreas transplantation as measured by additions to the wait list also continues to fall. The reasons for these trends are well defined in some areas but remain less clear in others. The OPTN continues to work to devise policy such as revised allocation strategies that it is hoped will remove existing structural barriers to pancreas transplantation and improve policy definitions and data collection to improve the understanding of donor quality and pancreas transplant outcomes. These efforts are designed to address the UNOS and OPTN strategic goal of increasing the number of transplants and providing accurate assessments of system and program performance.

Disclosures The data reported here have been supplied by the United Network for Organ Sharing (UNOS) as the contractor for the Organ Procurement and Transplantation Network (OPTN). The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy of or interpretation by the OPTN or the US Government.

Cross-References

- ▶ Donor Evaluation and Procurement
- ▶ Surgical Complications of Pancreas Transplant
- ▶ Surgical Technique of Pancreas Transplantation

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Medical Benefits of Pancreas Transplantation

Larry B. Melton

Contents

Abstract

The purpose of pancreas transplantation is to normalize the blood sugar of the recipient and minimize the secondary complications of diabetes. Data from the DCCT trial clearly showed that intensive blood sugar control was of long-term benefit in decreasing the secondary complications of diabetes. The incidence of retinopathy, nephropathy, and neuropathy is reduced in patients with intensive blood sugar control. As a more physiologic method of controlling blood sugar than insulin injection or an insulin pump, and addressing other functions of the endocrine pancreas, transplantation of the pancreas is superior to exogenously administered insulin. The transplanted pancreas will provide near-normal response to dietary intake. Numerous studies now support the fact that in addition to control of the blood sugar of diabetic patients, there are benefits seen in the areas of retinopathy, neuropathy, nephropathy, vascular disease, mortality, and quality of life.

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Pancreas transplant · Glucose control · Diabetic nephropathy · Diabetic retinopathy · Diabetic neuropathy · Pancreas transplant mortality · Pancreas transplant cardiovascular disease · Neuropathy and mortality

Introduction

Diabetes is a major contributor to morbidity and mortality of the population in the United States. Approximately 30 million people in the United States have diabetes and an additional 1.4 million are diagnosed annually. About 12% of the population over the age of 20 has diabetes and 26% of those over the age of 65 are diabetic. Diabetes is a direct or contributing cause of death for over 230,000 Americans each year and is responsible for over $245 billion in healthcare costs (ADA website 2016). Treating diabetes and its complications occupies the time of a large segment of the medical community on a daily basis. In addition, individuals with diabetes suffer significant medical, social, and economic repercussions from the disease. Therefore, any intervention that offers an opportunity for improved control or potential cure for diabetes is of interest to a large number of people and many organizations in this country.

The first pancreas transplant was performed at the University of Minnesota in 1966 (Kelly et al. 1967). Since that initial transplant, many variations of technique have been introduced and many studies have been done to assess the effectiveness of the pancreatic allograft. It is not felt that all diabetics are candidates for pancreatic transplantation because of the risks of immunosuppression, the potential complications of the surgery, and the relative ease with which the disease may be controlled in some patients. The official recommendation from the American Diabetes Association is that pancreas transplantation be considered for those patients who are to (1) undergo kidney transplantation for end-stage renal disease; (2) have frequent and severe metabolic complications requiring medical attention, incapacitating clinical and emotional problems with exogenous insulin administration; and (3) have consistent failure of exogenous insulin to prevent acute complications (American Diabetes Association 2006).

Transplantation of the pancreas has been shown to be of benefit for many of the secondary complications of diabetes. There is a clear benefit for blood sugar control, nephropathy, retinopathy, neuropathy, mortality, as well as quality of life. Although there are suggestions of benefit, the effects on cardiovascular disease and gastroparesis are still unclear. Part of the problem with determining the effect of pancreatic transplantation on these parameters is the length of time necessary to follow these patients to determine results and the survival of the pancreas graft itself. This chapter will review data that addresses the effect of pancreas transplantation on the secondary complications of diabetes.

Blood Sugar Control

From the outset, transplantation of the pancreas seemed destined to offer a "cure" for diabetes mellitus. Diabetes was known to originate from failure of the pancreatic beta cells, and replacing the whole pancreas was felt to be the answer for diabetic patients. The success of pancreatic transplantation has always been thought of in terms of controlling blood sugar.

In 1981, Sutherland et al. reported that diabetic patients who received segmental pancreas transplants had improved blood glucose levels after transplant, and this control seemed to continue to approach normal over the course of time. Fasting blood sugars in these patients were normal with near-normal glucose tolerance tests. In a report by Ostman et al. (1989), they compared the metabolic profiles of five nondiabetic end-stage renal disease patients who received kidney transplants with five diabetic patients who had end-stage renal disease and received combined kidney/pancreas transplants. The pancreas in these patients was placed intraperitoneally with the exocrine secretion diverted through a pancreaticojejunostomy with a Roux-en-Y loop. Blood glucose

Table 1 Parameters of pancreas and kidney graft function from 3 months to 10 years after simultaneous pancreas/kidney transplantation

	3 months	1 year	3 years	5 years	10 years	
	($n = 38$)	($n = 38$)	($n = 38$)	($n = 38$)	($n = 38$)	P
Fasting blood glucose (mg/dl)	78 ± 2	81 ± 2	82 ± 2	84 ± 2	91 ± 2	$<0.01^{a,b,c,d,e}$
HbA_{1c} (%)	4.6 ± 0.1	4.9 ± 0.1	4.9 ± 0.1	5.0 ± 0.1	5.3 ± 0.2	$<0.001^{f,a,b,d,g,h}$
120 min glucose (mg/dl)	118 ± 7	122 ± 9	110 ± 9	118 ± 9	150 ± 13	$<0.05^{d,g,i}$
Normal glucose tolerance (%)	67	56	68	66	37	$<0.05^{b,g,i}$
BMI (kg/m^2)	21.1 ± 0.4	21.9 ± 0.5	22.4 ± 0.5	22.8 ± 0.5	23.5 ± 0.7	$<0.05^{j,a,b,c,d,g}$
Fasting insulin (μU/ml)	21 ± 2	23 ± 2	18 ± 1	18 ± 1	16 ± 1	$<0.05^{d}$
$AUC_{insulin}$ (μU/ml×min)	11,735 ± 1365	11,754 ± 985	11,215 ± 886	11,801 ± 995	11,772 ± 1074	Ns
Incremental insulin $\Delta I_{30}/\Delta G_{30}$ (μU/ml)	221 ± 50	176 ± 28	157 ± 28	157 ± 22	168 ± 36	Ns
HOMA-IR	4.1 ± 0.4	4.5 ± 0.5	3.7 ± 0.3	3.7 ± 0.3	3.5 ± 0.3	Ns
Matsuda-deFronzo ISI	3.6 ± 0.4	2.9 ± 0.2	3.5 ± 0.3	3.1 ± 0.2	3.2 ± 0.3	Ns
S-creatinine	1.3 ± 0.1	1.3 ± 0.1	1.4 ± 0.1	1.5 ± 0.1	1.5 ± 0.1	Ns

Mean ± S.E.M. ANOVA with repeated measurements
Dieterle et al. (2007); with permission
[a]3 months versus 5 years
[b]3 months versus 10 years
[c]1 year versus 5 years
[d]1 year versus 10 years
[e]1 year versus 3 years
[f]3 months versus 1 year
[g]3 years versus 10 years
[h]3 years versus 5 years
[i]5 years versus 10 years
[j]3 months versus 3 years

levels monitored over 24 h were identical in the two groups. When plasma insulin, C-peptide, and glucagon levels were compared, the diabetic patients had significantly higher levels than the controls as would be expected with the systemic venous blood drainage.

Morel et al. (1991) published results of blood sugar and glycosylated hemoglobin A1 in a group of diabetic patients with at least 2 years of follow-up. They were compared to a control group of diabetics, pancreas transplant patients with failed grafts, and nondiabetic kidney transplants. The hemoglobin A1c was normal in most of the patients with a functioning transplant although in a few the readings were elevated to levels that would be considered diabetic. However, by 5 years, none of those with a functioning pancreas transplant had elevations in the hemoglobin A1c. Six patients were selected for long-term monitoring of their hemoglobin A1c because they had continuously normal values from the time of transplant. Over the course of 5 years, their values remained entirely normal.

A more long-term study was reported in 2007 where results of pancreas transplants after 10 years were described (Table 1, Dieterle et al.).

The authors showed that although fasting blood glucose was normal in a total of 38 subjects, the absolute values tended to rise over the course of 10 years with statistically significant increases at each measurement interval. In addition, blood sugar measured 120 min after oral administration

of 100 g of glucose was increasingly abnormal as well. By the end of 10 years, about a fourth of patients had abnormal glucose tolerance tests and another fourth had glucose tolerance tests that were consistent with a diabetic state. Only about 50% of patients remained completely normal. While this speaks to gradual loss of transplant pancreas function over time, likely related to a low-grade immunologic process, there are still a significant number of patients that have good to excellent transplant pancreas function. Some of those that were showing evidence of functional loss still continued to have an adequate response of the transplant to the usual daily stimuli.

Robertson et al. (1999) published on a series of patients studied at the University of Minnesota and at the University of Washington. There were a total of 16 patients that had received a whole or segmental pancreas transplant, some of whom had also received a kidney transplant. Patients had been transplanted between 10 and 18 years previously, and none were taking medications for hypoglycemic control. They were matched with 16 normal patients for sex, age, and BMI. There were no differences in fasting blood sugar or hemoglobin A1C between the groups.

The same findings were reported by Mora et al. (2010) analyzing patients that undergone combined kidney/pancreas transplantation with survival of the pancreas for at least 15 years. There were a total of 16 patients in this cohort. Of that group, two required low doses of insulin although they had normal C-peptide levels, and two were lost to follow-up. All patients had systemic venous drainage of the pancreas transplant. Of the 12 patients that were analyzed, all had normal fasting blood sugars and hemoglobin A1C values. Although these values were normal, when the patients were given an oral glucose tolerance test 15 years post-transplant, only 50% were normal, while 33% were classified as diabetic, findings consistent with those reported previously by Dieterle et al. (2007).

A number of investigators have observed higher insulin levels compared to controls both at baseline and after stimulation in pancreas transplant recipients. The higher baseline insulin levels are, in part, explained by the systemic venous drainage of the pancreas allograft. This phenomenon is not noted in patients whose pancreas transplant has its venous drainage into the portal vein. The administration of steroids has also been implicated in the relative insulin resistance and, perhaps, in the higher insulin levels. Of interest, C-peptide levels have been noted to be normal in pancreas recipients, regardless of the method of systemic drainage (Carpentier et al. 2001). Since one would expect that there has to be a unity between the insulin and C-peptide levels, the explanation of the discordant measurements may be related to peripheral insulin resistance as well as a difference in clearance of insulin as opposed to C-peptide. While insulin and C-peptide are secreted in a 1:1 ratio into the portal circulation, there is a difference in the plasma half-lives of the two peptides (Horwitz et al. 1975). This difference may be magnified by other factors that affect metabolism or excretion of the peptides including the presence of immunosuppressive drugs.

Nephropathy

Diabetic nephropathy is a leading cause of end-stage renal disease. According to the latest Scientific Registry of Transplant Recipients report, 28.6% of the transplants done in 2014 were for diabetic patients (2016). It is generally known that end-stage renal disease from diabetes usually occurs after a long period of time. End-stage renal disease is present in both type 1 and type 2 diabetic patients. However, the number of type 2 diabetics exceeds that of type 1 diabetics and, therefore, represents a disproportionate percentage of those on dialysis and on the waiting list for kidney transplants.

The pathology of kidney failure in diabetic patients can be demonstrated 3–5 years after the diagnosis of diabetes is made and is characterized by thickening of the glomerular basement membrane and by mesangial expansion. The clinical manifestation is the appearance of microalbuminuria in 40–50% of type 1 diabetics followed several years later by frank proteinuria in excess of 300 mg/24 h. In about 10 years, half of these patients will reach end-stage renal

disease. It is thought that the microalbuminuria in type 2 diabetics may be less predictive of renal failure since it is more likely to be related to chronic coexisting disorders like hypertension or heart disease. Regardless of etiology, the presence of microalbuminuria heralds the presence of kidney disease and this will be progressive. Later, the classic lesion of nodular glomerulopathy, or Kimmelstiel-Wilson disease, may be seen in the glomeruli of diabetic patients. Most of the time, the diagnosis of diabetic glomerulopathy is made on clinical grounds, without biopsy, considering the history, presence of retinopathy or neuropathy, normal-sized kidneys on sonography, proteinuria, and a relatively benign urinary sediment.

Evidence that blood sugar control is of paramount importance in preventing, or at least retarding, the development of diabetic nephropathy comes from clinical trials that compare the onset of microalbuminuria and rise in the serum creatinine between patients that have intensive control vs conventional control of their diabetes. In multiple studies, a correlation has been shown between control of diabetes and rate of decline of kidney function (Hovind et al. 2001; Pirart 1978). In the study by Hovind et al., there was a clear association between hemoglobin A1C and control of hypertension and the loss of glomerular filtration rate. Those patients that had lower hemoglobin A1C levels and better control of their hypertension also had a slower decline in glomerular filtration rate (Fig. 1). In the DCCT study, two groups of diabetic patients were compared. Those in the primary prevention group were required to have less than 40 mg of albuminuria in 24 h, whereas those in the secondary prevention group had less than 200 mg in 24 h. Each of these groups was divided into an intensive and conventional

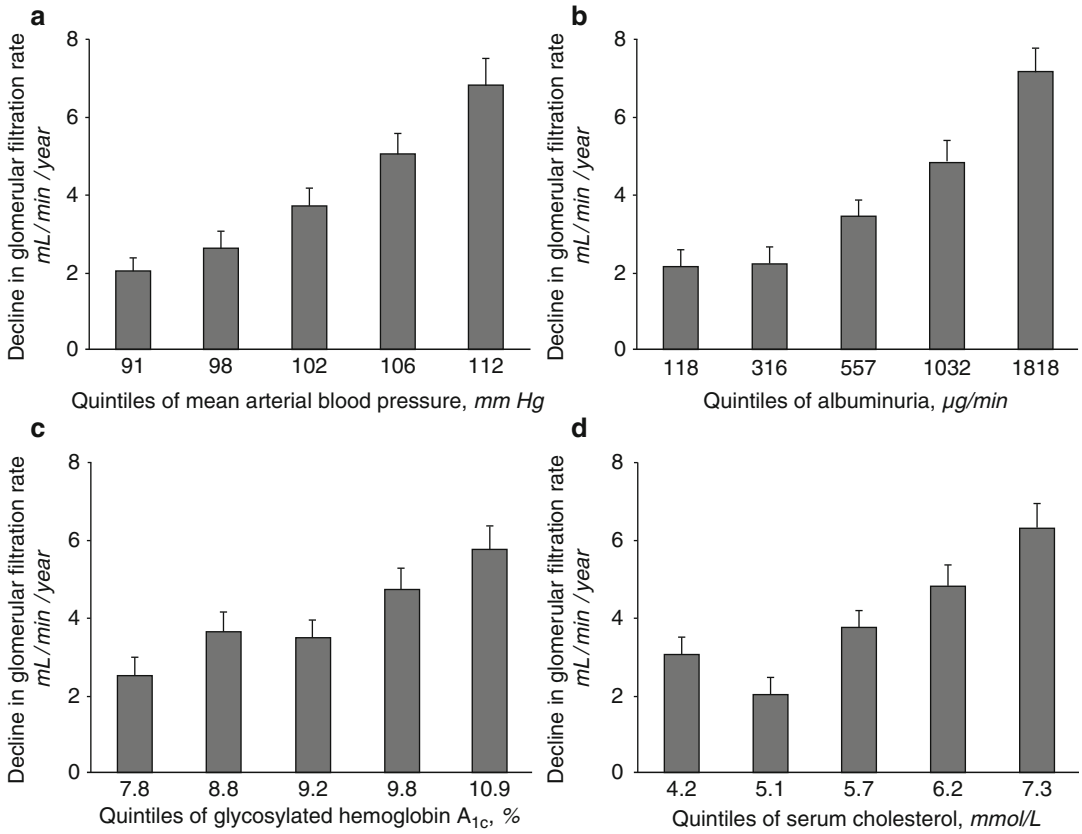

Fig. 1 Impact of mean arterial blood pressure, glycosylated hemoglobin A1c, albuminuria, and serum cholesterol on the decline in GFR ($P < 0.001$ for each factor) (Hovind et al. 2001; with permission)

treatment arm. The average time of follow-up was 6.5 years (range of 3–9 years). At that time, the trial was terminated because of a clear advantage in the intensive control group (DCCT 1993). Patients that received intensive diabetic control in both the primary and secondary groups had significantly slower development of proteinuria.

It is known that when normal kidneys were transplanted into diabetic patients, the kidneys will begin to show histologic changes related to the presence of the diabetic environment within a few years. Mauer et al. (1983) demonstrated that virtually every diabetic lesion developed in kidneys was transplanted into diabetic patients. The first of these to appear on routine post-transplant biopsies is glomerular basement membrane abnormalities and mesangial expansion. These can be seen as early as 2 years after kidney transplantation.

Bohman et al. (1985) reported that in diabetic patients who received a combined kidney/pancreas transplant or a pancreas-after-kidney transplant, diabetic nephropathy was prevented during the follow-up period ranging from 2 to 8 years. Interestingly, it was shown by Fioretto et al. (1998) that if a pancreas was transplanted into a diabetic patient without end-stage renal disease and kidney biopsies were done at the time of transplant and at 5 and 10 years post-transplant, the preexisting diabetic lesions progressively improved so that at the 10-year biopsy, the glomeruli appeared normal. Measurements taken from the glomerular basement membrane showed that for all eight patients, the measured parameters were normal or approached normal at the 10-year mark. Creatinine clearance fell from baseline when measured at 5 years but remained stable after that. As the authors point out, this was likely the result of cyclosporine immunosuppression and served as a confounding variable for the study. There was some interstitial damage noted in the biopsies at 5 years that was presumed to be from the immunosuppression. Surprisingly, many of these interstitial changes had shown improvement in the 10-year biopsy samples. (There were 13 patients in the original cohort but two progressed during the first 5 years after pancreas transplant and required kidney transplants, two others lost their pancreas transplants and returned to insulin therapy, and one declined to participate in the 10-year follow-up.)

Retinopathy

Diabetes is a leading cause of blindness in the United States. From 2005 to 2008, of Americans with diabetes who were 40 years of age or older, 28.5% had diabetic retinopathy. It is the leading cause of vision loss and blindness among working-aged adults (2016). The ability to prevent, control, or reverse the retinopathy caused by diabetes would positively impact millions of lives.

One of the major complications with determining the effect of pancreas transplantation on the course of diabetic retinopathy is that there are so many confounding influences. Retinopathy and visual acuity may be influenced by:

The presence of preexisting lesions
Continued laser therapy after transplantation
Correction of the uremic state
Cataract formation and/or extraction
Cytomegalovirus disease
Ischemic optic neuropathy
Uncontrolled hypertension

In addition, authors are not consistent in the analysis of retinopathy. Some report changes in various retinal scores. Others use visual acuity as a measure. As a result, there are conflicting reports in the literature about diabetic retinopathy after pancreas transplantation. In this regard, some studies have reported no effect of pancreas transplantation on diabetic retinopathy, while others report either stabilization of the less severe degrees of retinopathy or frank improvement in diabetic retinopathy scores. There are reports that do not support any effect of pancreas transplantation on retinopathy. Many of these had a short duration of follow-up; in some there was already significant retinopathy, and in all many of the factors listed above served as confounding variables so that no effect was discerned (Petersen and Vine 1990; Wang et al. 1994; Bandello et al. 1992).

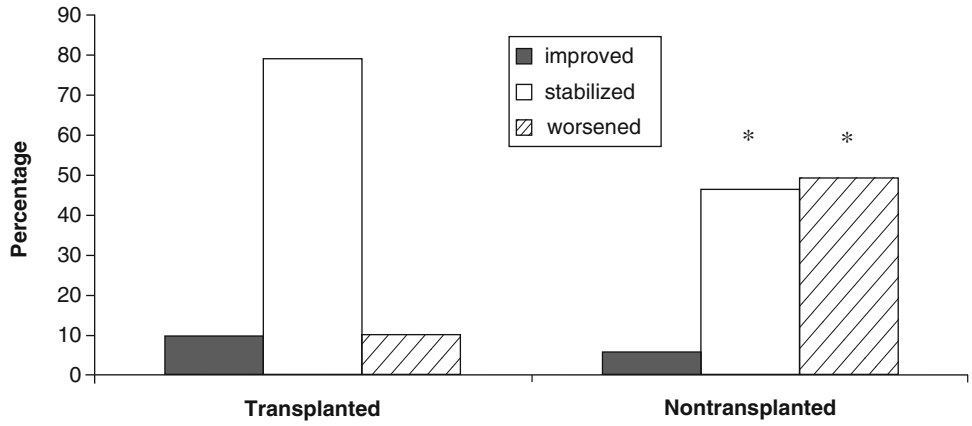

Fig. 2 Percentage of patients with improved, stabilized, or worsened diabetic retinopathy in the transplanted and non-transplanted groups. *$P < 0.01$ versus transplanted (Giannarelli et al. 2005; with permission)

Ramsay et al. (1988) reported on 22 patients with diabetic retinopathy that received a pancreas transplant and compared them with a control group of 16 patients that received a pancreas transplant that failed. After 24 months of follow-up, there was no difference in progression of retinopathy. However, between 24 and 72 months of follow-up, 70% of the group that still had a functioning pancreas transplant were shown to have stable eye findings, while the control group continued to progress, and at 60 months, only about 25% had stable retinopathy. There was no difference in loss of visual acuity between the groups.

In contrast, Konigsrainer et al. (1990) reported progression of retinopathy in two groups similar to those reported by Ramsay et al. In their report, there were 39 eyes in the pancreas transplant group and 23 in the group that had lost their pancreas and served as the control. There were more patients on antihypertensive medications in the functioning pancreas group and more of them (19 vs. 4) had a functioning kidney transplant as well. Over the course of the observation period that ranged from 14 to 70 months, they noted that 15% of the patients with a functioning pancreas had regression of the retinopathy, 77% stabilized, and only 8% progressed. In the control group, 70% stabilized and 30% progressed.

The results of combined kidney/pancreas transplantation on retinopathy were described in 48 patients in a report by Giannarelli et al. (2005). They were followed for 6–60 months with a control group of 43 non-transplanted type 1 diabetic patients that was followed for a comparable period (8–66 months). Patients were evaluated in a blinded fashion, and there was no difference in retinopathy between the groups at the onset of the study. Figure 2 shows that at the end of the observation period, 90% of those with a functioning transplant showed stabilization or improvement in the retinopathy, whereas 50% of the control group had deterioration.

In 2006, Giannarelli et al. published a follow-up report on 33 patients that received a pancreas transplant alone compared to 35 type 1 diabetic patients who were not transplanted. The pancreas transplants were done through an intraperitoneal approach using the portal vein-enteric drainage technique. All 33 of the transplanted patients obtained normal blood sugars. Retinopathy was improved or stabilized in 91% of the transplanted patients and only 43% of the non-transplanted controls. Deterioration was seen in only 9% of the transplanted patients, and in all of these, there was advanced retinopathy at the time of transplant. Fifty-seven percent of the non-transplanted patients had deterioration.

It now seems that the majority of investigators recognize that a functioning pancreas transplant and maintenance of a normal glycemic environment will at least stabilize less severe diabetic retinopathy. A few have published results

indicating that retinopathy may actually improve over time although visual acuity will, at best, remain unchanged (Chow et al. 1999). Given that some 10,000 diabetic patients annually will succumb to blindness, this represents a significant advantage to those who maintain normal glucose homeostasis through a functioning pancreas transplant.

Neuropathy

Diabetic neuropathy is common as a secondary complication of both type 1 and type 2 diabetes mellitus. It takes years to develop and is frequently present in combination with other complications of diabetes such as retinopathy and accelerated vascular disease. It commonly affects the motor and sensory as well as the autonomic nervous system. Manifestations include varying degrees of tingling or numbness in the toes, feet, legs, fingers, and hands. Among the autonomic manifestations are those that involve gastrointestinal and cardiac dysfunction.

Many of the studies involving effects of pancreas transplantation on diabetic neuropathy suffer from the same limitations seen in the studies on retinopathy. Beneficial effects on neuropathy will take place slowly, over long periods of time, and it is therefore a challenge to establish improvements as the result of normoglycemia.

Kennedy et al. (1990) reported on a series of patients who received pancreatic transplants. There were 61 patients in the transplant group and 48 non-transplanted patients with type 1 diabetes. The control patients were either listed for a pancreas transplant or had one that had failed within 3 months. Of the patients with a pancreas transplant, 26 also had a renal transplant. Nineteen had received the renal allograft prior to pancreas transplantation and seven received a combined kidney/pancreas transplant. They were studied before and at about 12 months after transplantation. Subsets of the group were also studied at 24 and 42 months. Twelve months post-transplant, motor and sensory nerve conduction velocities had improved in those patients receiving pancreas transplants. There were nonsignificant improvements seen at 24 and 42 months post-transplant. The authors suggested one reason for this was the smaller numbers of patients available for study at the longer time intervals. In contrast, neuropathy in the control group progressed over 42 months of the study. With respect to individual patients, a greater percentage of those with pancreatic transplants improved and those in the control group deteriorated during the period of observation. An earlier study by Orloff et al. (1990) in which diabetes was induced in rats with alloxan and then some were transplanted with pancreata demonstrated that the numbers of myelinated axons increased, glycogen deposits decreased, and the degeneration of axons reversed in the transplanted rats. Since the transplants in these animals were done early after the onset of diabetes, the argument made by Kennedy et al. related to the degree of neuro- and microvascular deterioration may be accurate.

Navarro et al. reported on a series of patients in 1996 with measurements of neuropathy expressed as the total neuropathy score (TNS). The scores reflected worsening neurologic function as measured by cardiorespiratory reflex and nerve conduction velocity. Those with minimal neurologic impairments had a TNS of 0, those with moderate impairment had a TNS of 1, and those with severe impairment had a TNS of 2. Patients had a functioning pancreas transplant, a pancreas that had failed within the first 3 months, or no pancreas transplant. Figure 3 shows the survival curves over 132 months for non-transplanted diabetics by TNS score. It is clear that the worse the neuropathy, the worse the patient survival. In Fig. 4 the survival curves for diabetic patients with TNS of 1 or 2 are shown for the various transplanted groups. Pancreas transplantation led to better survival in patients regardless of the degree of neuropathic impairment.

A more extensive report (Navarro et al. 1997) detailed the follow-up of 115 diabetic patients that received a pancreas transplant and had a functioning graft at 12 months with a control group of 92 diabetic patients that had received a kidney transplant only, were waiting on a pancreas transplant, or who had a pancreas graft that had failed within the first 3 months after transplant. Mean

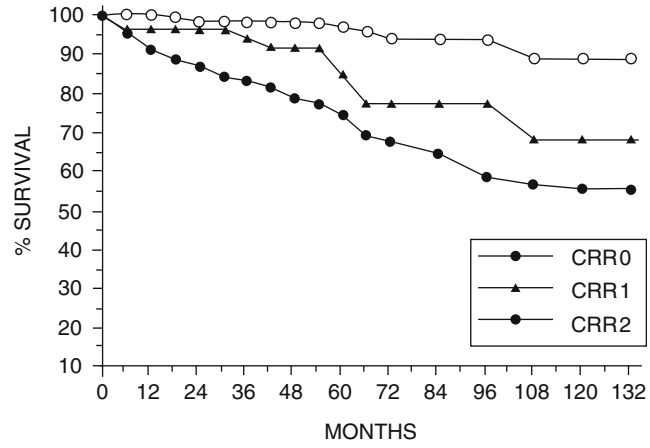

Fig. 3 Survival curves for diabetic patients with no abnormal cardiorespiratory reflex tests (CRR 0; $n = 128$), one CRR test abnormal (CRR 1; $n = 58$), and two CRR tests abnormal (CRR 2; $n = 359$) (Navarro et al. 1996; with permission)

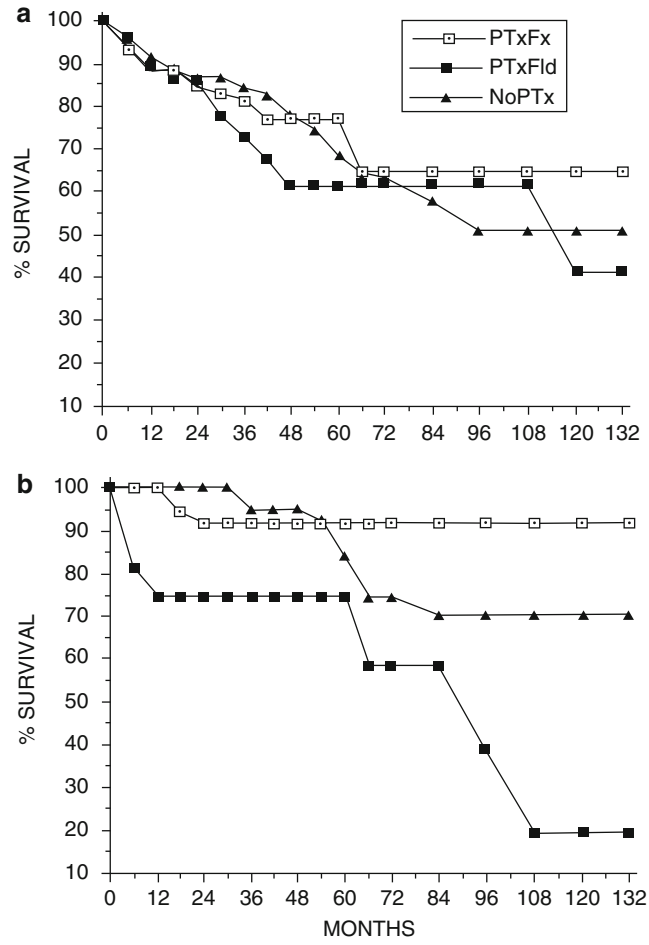

Fig. 4 Survival curves for diabetic patients with TNS 2 (**a**) who had a functioning pancreas transplantation (PTxFx, $n = 87$), a pancreas transplantation that had failed within 3 months (PTxFld, $n = 33$), or no pancreas transplantation (NoPTx, $n = 121$) and for diabetic patients with TNS 1 (**b**) who had a functioning pancreas transplantation (PTxFx, $n = 53$), a pancreas transplantation which had failed within 3 months (PTxFld, $n = 19$), or no pancreas transplantation (NoPTx, $n = 53$) (Navarro et al. 1996; with permission)

duration of diabetes in both groups was about 21 years. Variable numbers of patients were available on an annual basis for follow-up. At 10 years follow-up, all of the measures of neuropathy had improved in the transplanted patients while the controls continued to deteriorate. Diabetic patients that had functioning allografts did much better in all areas of neurologic evaluation with the various parameters stabilizing. Patients with pancreas transplant alone had more consistent improvement and, as the authors indicate, had less neuropathy at the beginning of the study. This improvement was the result of correction of the diabetic state since there was no uremic environment present and, therefore, no renal transplant or uremic neuropathy, a finding also reported by other authors (Solders et al. 1992).

In other patients, combined kidney/pancreas transplantation was performed and nerve conduction studies followed during the time of normoglycemia and, for several years after the pancreas graft failed, allowing each patient to serve as their own control (Martinenghi et al. 1997). While the pancreas was functional in these patients, nerve conduction velocity measurement improved. After the pancreas transplant failed, the nerve conduction velocities began to deteriorate.

Finally, there is a recent publication in which skin biopsies of the thigh were done and epidermal nerve fiber counts performed. Vibration perception thresholds, nerve conduction velocities, and standard tests of autonomic nerve function were used to assess neuropathy (Havrdova et al. 2016). Blood sugar control in the pancreas transplant patients was excellent as measured by hemoglobin A1c. There were no improvements seen in epidermal nerve fiber density, vibration perception, or autonomic nerve function throughout the 8 years of follow-up except in 1 out of 12 study patients whose nerve density progressively improved. The only demonstrated functional improvement was in median nerve motor conduction velocity. The authors suggest that their results may run counter to other studies that show improvement because of the possible inclusion of younger patients with less severe nerve and microvascular damage in other studies. They also discuss other potential pathophysiologic mechanisms to explain these differences. They suggest that the establishment of euglycemia in diabetic patients should be done early, before the severity of long-term disease has damaged the nervous system beyond repair.

In spite of some reports to the contrary, the weight of the evidence favors some improvement of neuropathy with pancreas transplantation. Duration and degree of damage may modulate this to some extent. This is consistent with the findings of the Diabetic Control and Complications Trial showing that intensive glucose control ameliorates the secondary complications of diabetes (1993).

Cardiovascular Disease

Cardiovascular disease is a leading cause of death among patients with end-stage renal disease (USRDS 2015). It is well known that the accelerated rates of atherosclerosis and heart disease in diabetic patients, particularly those with end-stage renal disease, lead to higher mortality rates in this population. Cardiovascular disease accounts for 30% of the first year deaths and about 25% of the deaths in years 1–5 in the transplant population (Checka 2000; Andre et al. 2015). As such, prevention of cardiovascular disease is of paramount importance in improving the survival rates of diabetic patients with end-stage renal disease.

Most early studies of pancreas transplant patients concentrated on glycemic control, influence on secondary complications of diabetes, and on changes in metabolic parameters. As further work continued on the benefits of pancreas transplantation, interest in the effects on other organ system dysfunction developed.

One of the early studies on cardiac function in a pancreas transplant population was reported by Gaber et al. (1995a). Diabetic patients that received combined kidney/pancreas, pancreas-after-kidney, or kidney transplant alone had echocardiography performed preoperatively and at 6 and 12 months postoperatively. The patients who received pancreas transplants had improved cardiac parameters compared to their baseline values and to the kidney-alone transplant patients. The findings by Gaber et al. were duplicated in a

study by Coppelli et al. (2003). In their study, a small but significant increase was seen in the left ventricular ejection fraction of patients undergoing pancreas transplantation. The most impressive result, however, was that in this cohort, the left ventricular mass declined significantly at 6 months after transplantation.

In 2000, Fiorina et al. published a report in which they compared diabetic patients receiving a combined kidney/pancreas transplant and compared them to diabetic patients receiving a kidney-alone transplant. All patients with coronary artery disease were excluded. Radionuclide left ventriculography was performed on the patients at 6 months, 2 years, and 4 years. While there were no differences in the left ventricular ejection fraction at 6 months and 2 years, at 4 years, there was a clear division in the patients. There was progressive improvement in the kidney/pancreas transplant group throughout the 4 years of the study but improvement in the kidney-alone group only at 6 months of follow-up. This was a direct effect on the cardiac and/or neuropathic abnormalities since there was no coronary artery disease in either group. This same group (La Rocca et al. 2001) followed up the initial report with a second study confirming their initial results and also showing a better survival rate and fewer cardiac events in the combined kidney/pancreas transplant patients compared to the other two groups.

Directly addressing the issue of coronary atherosclerosis, Jukema et al. (2002) measured the mean segment diameter of coronary arteries with sequential angiography. Thirty one patients had pre- and post-transplant angiography. Post-transplant repeat angiography was required to be done after a minimum of at least 2 years and ranged up to 5.5 years. Patients who had functioning pancreas transplants were compared to patients who had early loss of their pancreas grafts. The mean segment diameter of coronary vessels deteriorated in the six patients with no functioning pancreas transplant at a rate almost twice that of the 25 patients who had a functioning pancreas graft.

Looking at peripheral vascular disease, Larsen et al. (2004) examined the carotid intima-media thickness in a group of pancreas transplant recipients versus diabetic patients with no nephropathy, in nondiabetic kidney transplant recipients, and in normal controls. After 2 years, the pancreas transplant group had significant improvement in the mean intima-media carotid thickness compared to the pre-transplant values. In addition, the pancreas transplant group was not statistically different from the normal controls nor the diabetic patients without nephropathy. Only the nondiabetic kidney transplant group had significantly better scores.

Conversely, in a report by Nankivell et al. (2000), progression of atherosclerosis in carotid arteries was examined by duplex ultrasonography. In patients who had a combined kidney/pancreas transplant, there was an increase in the measured plaques from their pre-transplant values over the ensuing 7–10 years. Of note, there was no control group in this study so it is difficult to know whether the pancreas transplant made a significant difference in progression of the carotid disease.

Miscellaneous Metabolic Abnormalities

Following pancreas transplantation, a variety of metabolic changes appear.

Among these are hyperinsulinemia and various lipid abnormalities. Since most patients with pancreas transplants receive them in conjunction with a renal transplant for end-stage renal disease, disorders of bone metabolism and hypogonadism that may be present are recognized as long-standing results of the end-stage renal disease. Extraneous influences may affect these body systems, such as immunosuppressive medications or other preexisting recipient abnormalities. Pancreas transplantation does not seem to bear directly on these disorders. In fact, hypogonadism associated with end-stage renal disease typically improves after kidney transplantation. However, there may be other contributing factors related to diabetes such as neuropathy or vascular disease that affect sexual function in both men and women. Metabolic bone disease is more complicated and is intertwined with vitamin D metabolism, age, gender, the hyperparathyroidism of

Table 2 Metabolic characteristics of patients with portal-enteric and systemic-bladder drained pancreas allografts at 6 and 24 months after transplantation

	Portal-Enteric		Systemic Bladder	
	6 mos	24 mos	6 mos	24 mos
	($n = 19$)	($n = 7$)	($n = 28$)	($n = 17$)
Body mass Index (kg/m^2)	24.4 ± 0.78	25.2 ± 1.21	25.1 ± 1.34	24.3 ± 1.17
Hemoglobin A_{Ic} (%)	5.9 ± 0.51	5.7 ± 0.36	6.0 ± 0.66	5.6 ± 0.2
Hematocrit (%)	39.4 ± 2.3	41.8 ± 3.2	40.1 ± 1.67	37.7 ± 1.3
Serum creatinine (mg/dL)	1.5 ± 0.18	2.8 ± 0.81	1.9 ± 0.25	1.8 ± 0.12
Fasting plasma glucose (mg/dL)	85.5 ± 2.2*	98.4 ± 8.0	98.7 ± 3.5*	88.0 ± 2.5
Fasting plasma insulin (μU/mL)	11.0 ± 2.1†	7.9 ± 1.8†	55.3 ± 9.7†	38.8 ± 9.7†
Fasting plasma C-peptide (pmol/mL)	1.4 ± 0.41†	1.0 ± 0.18*	2.1 ± 0.21†	1.8 ± 0.26*
Fasting insulin:C-peptide ratio	6.92 ± 1.6†	6.31 ± 1.7*	20.89 ± 2.1†	15.13 ± 2.2*

Values are ± SEM
Gaber et al. (1995b); with permission
*$p \leq 0.05$
†p ^ 0.01 between groups at the same time points

renal disease, and the use of steroids or calcineurin inhibitors post-transplant (Larson 2004). Pancreas transplantation itself has, in fact, been associated with a reduction in fractures and increase in bone mass in some studies (Nikkel et al. 2013).

The two most prevalent metabolic issues after pancreas transplantation are hyperinsulinemia and dyslipidemia. A less common but particularly annoying complication is the presence of diabetes itself. On occasion, following pancreas transplantation, the recipient remains diabetic. The usual reason for this relates to the use of certain immunosuppressive medications. It can usually be corrected by changing the patient to a medication other than tacrolimus or by discontinuing the steroids. At times, there can be a recurrence of autoimmune type 1 diabetes (Larson 2004; Lauria and Ribeiro-Oliverira 2016).

Hyperinsulinemia occurs when the venous drainage from the pancreas directly enters the systemic circulation. This results from the common technique of exocrine drainage into the bladder and vascular anastomoses to the iliac artery and vein. While enteric exocrine drainage and venous drainage into the portal vein is a more physiologic system, it presents more significant technical complications, and most venous drainage is now systemic, even though the exocrine drainage of most pancreas transplants is enteric (Gruessner 2011).

Gaber et al. (1995b) compared diabetic patients that had pancreas transplantation done with exocrine drainage into a Roux-en-Y loop and venous drainage into the portal system, with patients having exocrine drainage into the bladder and venous drainage systemically (Table 2). Those who had systemic venous drainage had high insulin levels at both the 6- and 24-month time points. The fasting insulin/C-peptide ratio was also markedly elevated in this population.

Hyperinsulinemia is important because it has been implicated in the pathogenesis of hypertension (Ferrannini et al. 1987; Osei 1999) and ischemic heart disease (Despres et al. 1996). Insulin has been shown to stimulate arterial smooth muscle cell proliferation and induce migration of these cells from the media to the intima (Stout 1990). It has long been known to be directly related to hypertriglyceridemia and elevations in VLDL and inversely related to LDL (Stout 1990). In addition, insulin stimulates cholesterol synthesis within the arterial cells. All of this leads to progressive atherosclerosis. Whether the hyperinsulinemia of systemic venous pancreas drainage is adequately countered by the euglycemic state is problematic. While it is difficult to reconcile some of the seemingly contrary findings, the majority of studies support the benefits of pancreas transplantation in retarding the progression of heart and vascular disease even in the setting of hyperinsulinemia.

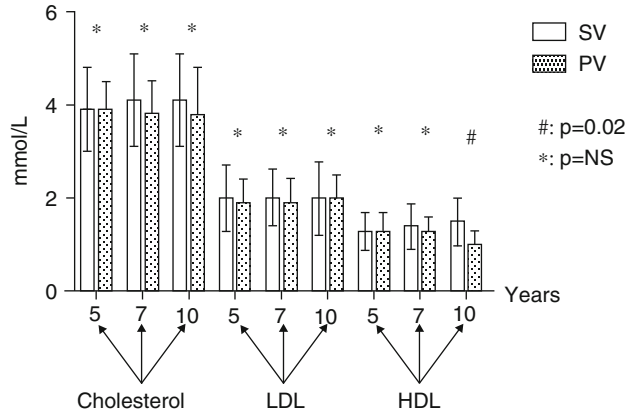

Fig. 5 Lipid profile in recipients with SV or PV pancreas grafts. Number of observations analyzed comparing SV versus PV groups, respectively, during follow-up intervals of 5, 7, and 10 years, respectively, for cholesterol (85 vs. 37, 54 vs. 34, and 18 vs. 23), HDL (87 vs. 35, 55 vs. 31, and 18 vs. 23), and LDL (85 vs. 34, 54 vs. 34, and 18 vs. 22) (Bazerbachi et al. 2012; with permission)

Most diabetics have abnormalities in lipid metabolism before transplant. There are multiple factors that influence this. Uncontrolled diabetes is characterized by hypercholesterolemia and hypertriglyceridemia. As blood sugars are brought under control, these lipids also return closer to normal values. Insulin is involved in regulating lipid metabolism in several ways. Low insulin levels lead to elevations in VLDL and LPL. Insulin resistance causes hypertriglyceridemia, low HDL, and elevated VLDL (Ginsberg and Goldberg 2001).

With regard to the hyperlipidemia, Forger et al. (1994) reported that HDL cholesterol was higher in diabetic patients with combined kidney/pancreas transplants compared to either diabetic or non-diabetic kidney transplant patients or non-transplanted controls. They explained their observations by lower postprandial triglycerides because of higher lipoprotein lipase activity in the kidney/pancreas transplant patients. They felt the improved lipid profile could be expected to counteract the atherosclerotic risk of long-standing diabetes.

Hughes et al. (1995) showed that patients with combined kidney/pancreas transplants that had portal venous drainage had a significant decrease in VLDL ApoB compared to the systemically drained group whose corresponding lipid fractions were increased at 6 and 12 months. However, Bazerbachi et al. (2012) followed patients with portal and systemic drainage for 10 years (Fig. 5). They reported that there were no differences in the lipid profiles at 5, 7, and 10 years. One of the problems with their study, and a confounding effect of most studies, is that the patients had been treated with lipid lowering agents. Unless patients have not been treated with antihyperlipidemic drugs, the differential techniques of venous drainage becomes difficult to ascertain. In addition, it may be that the longer the pancreas transplant is in place, physiologic adaptations occur that neutralize differences in lipid profiles seen earlier in the post-transplant course. Further, genetic differences in individuals may also change the absolute effect that kidney/pancreas transplantation has on the lipid profile. In general, it seems to be felt that there are higher lipid levels in the systemically drained population although there does not seem to be clear evidence that this relates to a higher incidence of heart or vascular disease. Observed benefits of pancreas transplantation, although insulin levels may be higher in the systemically drained population, may outweigh the theoretical disadvantages.

Mortality

Diabetes is known to have effects on multiple organ systems, and many of these affect the quality of life and life expectancy of those so afflicted.

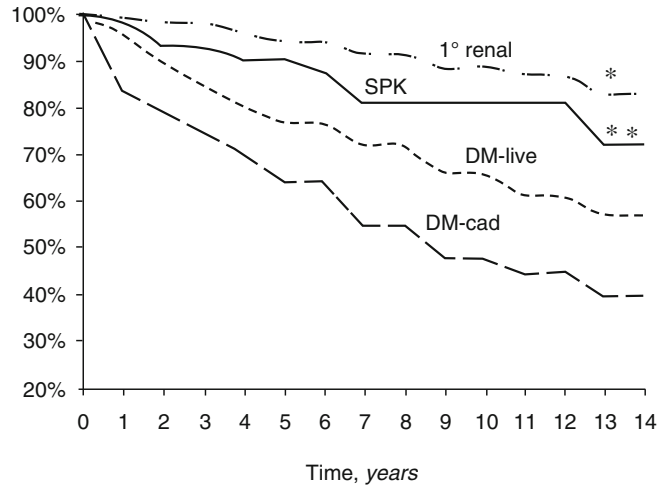

Fig. 6 Kaplan-Meier estimates of simultaneous pancreas-kidney (SPK), diabetic cadaveric (DM-Cad), live-donor (DM-Live), and the primary renal disease cohort (1 renal) transplant patient survival. *P=0.0029 1 renal vs. all others; **P=0.004 SPK vs. DM-Cad, DM-Live.

Diabetics have a shortened life span and those with end-stage renal disease bear an even heavier burden. Some estimates are that people with type 2 diabetes have a life span that may be shortened by as much as 10 years, while those with type 1 diabetes may be shortened by as much as 20 years (2016 diabetes.co.uk.html). If end-stage renal disease is present, the 5-year survival of diabetic patients, by some estimates, is only 30% (Ghaderian et al. 2015). There is evidence that pancreas transplantation may offer improved mortality, at least in those with end-stage renal disease.

In a study comparing diabetic patients with either kidney or combined kidney/pancreas transplantation, Navarro et al. (1990) reported that diabetic patients that had neuropathy had worse survival than those who did not. Furthermore, those who had a functioning pancreas transplant had significantly better survival while those who had a pancreas transplant that was lost within the first 3 months after transplant had survival rates lower than those who did not receive a pancreas transplant. This report was followed in 1996 (Navarro et al.) showing that the greater the degree of neuropathy correlated with worse survival (Fig. 3) and that the presence of a functioning pancreas transplant for more than 3 months gave a distinct survival advantage (Fig. 4).

Mortality was also addressed in a study by Becker et al. (2000). They compared nondiabetic patients with end-stage renal disease receiving kidney transplants with diabetic patients receiving either deceased donor, living donor, or combined kidney/pancreas transplants (Fig. 6). Consistent with findings reported by Navarro et al. (1990, 1996) the diabetic patients with combined kidney/pancreas transplants had a much longer survival than diabetics with either a living donor or deceased donor renal transplant. Only nondiabetic patients with renal transplants fared better. These data have been duplicated in other investigators as well (Gunnar et al. 1999; Ojo et al. 2001).

In the report by Ojo et al. (2001), they showed that the 10-year survival rate of diabetic patients with a combined kidney/pancreas transplant was equivalent to that of diabetic patients who received a kidney from a living donor. Furthermore, diabetics who received a deceased donor renal transplant had a 10-year survival that was almost 20% lower (Fig. 7). The leading cause of death in all groups was cardiovascular, although statistically lower in the combined kidney/pancreas group, and the second leading cause was infection which was statistically higher in that same group (Table 3).

La Rocca et al. (2001) described mortality curves for 130 patients who received combined

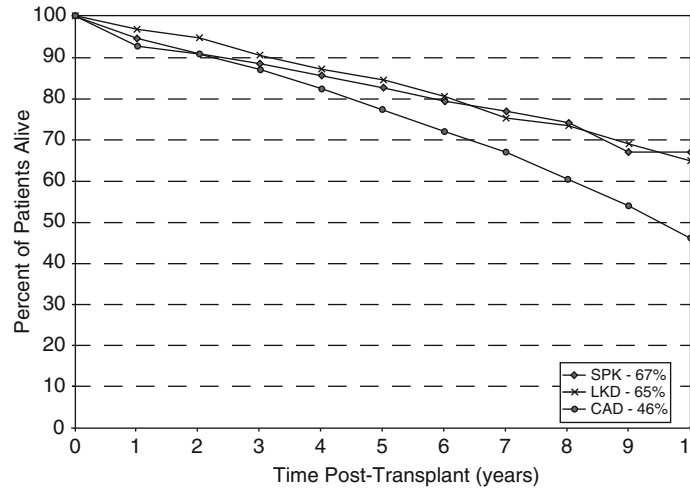

Fig. 7 Ten-year survival in three groups of kidney transplant recipients with end-stage nephropathy due to type 1 diabetes mellitus (Ojo et al. 2001; with permission)

Table 3 Causes of death (%) among patients with type1 diabetes mellitus according to treatment group, 1988–1997

	Treatment group			
Cause of death	SPK	LKD	CAD	Maintenance dialysis (wait-listed)
Cardiovascular[a]	33.4	46.9	42.5	48.6
Cerebrovascular[b]	7.1	3.1	6.1	6.7
Infection[b]	21.5	14.8	12.5	11.9
Malignancy[c]	3.3	3.1	1.8	0.4
Other	34.7	32.0	37.0	32.3

Ojo et al. (2001); with permission
[a]$P < 0.01$ for SPK compared each of the other groups
[b]$P < 0.05$ for SPK compared with LKD and CAD groups
[c]$P < 0.05$ for SPK compared with CAD and wait-listed dialysis groups

kidney/pancreas transplants, 25 diabetic patients with kidney alone, and 196 end-stage renal disease diabetic patients who remained on the waiting list for transplant. There were no demographic differences in the three groups. A subset of patients had radionuclide evaluation during the follow-up period, and there were no differences between the kidney/pancreas and kidney-alone transplant patients. At 7 years of follow-up the survival of the combined kidney/pancreas transplant patients was about 80%, while those of the kidney-alone transplants was 60%, and the wait-listed ESRD diabetic patients was 40%.

Reports from the International Pancreas Transplant Registry (Gruessner 2011) have consistently showed improvements in the survival rates of pancreas transplant patients in all categories. Pancreas transplant patient and graft survival now compare favorably with the corresponding survival rates for kidney transplants.

Conclusion

Pancreas transplantation has been performed since 1966. The objective was correction of the diabetic state, reversal or prevention of the secondary complications of diabetes, and returning patients to a normal life. It is a technically complicated procedure, is difficult to manage, and needs an experienced team with knowledge, understanding, and skill in the art as well as the science of medicine. When successful, it is life-changing. Survival rates of both patients and grafts are consistently improving. Complications such as hyperlipidemia, degree of blood sugar

control, vascular disease, and retinopathy or neuropathy improvement all have good scientific evidence suggesting stabilization if not improvement. The arguments about efficacy and utility pale beside successes of the procedure and the improved quality of life of the patients.

There are other alternatives being investigated for treatment of diabetes. These include gene therapy, glucose sensors, and islet cell transplantation. The optimal choice remains unclear and technical issues still offer challenges. Whatever the treatment, the data is clear that intensive control of hyperglycemia offers distinct long-term advantages for the diabetic patient.

Cross-References

- Follow-Up Care of the Pancreas Transplant Recipient
- Surgical Complications of Pancreas Transplant
- Surgical Technique of Pancreas Transplantation

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Anatomy and Physiology of the Pancreas

M. Rosenzweig and E. Grodstein

Contents

Abstract

Mastery of the anatomy and physiology of the pancreas is fundamental in understanding the concepts involved in Pancreas transplantation. Normal anatomy and physiology are critical to appreciating the pathology of any organ system. The indications for transplantation require knowledge of both the normal and pathological states of the involved organ. A firm grasp of the blood supply, drainage, surrounding visceral anatomy, as well as the anatomical considerations of endocrine and exocrine pancreatic physiology are essential to graft function and survival. While this chapter's main focus is anatomy and physiology, the transplantation of the pancreas requires a multidisciplinary approach. As such, there are a number of topics that crossover with other chapters of this text. We will highlight those specific subjects and how they pertain to

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the core of this section. Upon completion of this chapter, the reader should feel comfortable with pancreas anatomy and physiology and how these concepts will impact pancreatic transplantation.

Keywords
Endocrine pancreas · Exocrine pancreas · Diabetes · Islet cells · Proteases

Introduction

The pancreas is an intricate organ with diverse function and the complexities of the pancreas have been studied substantially. The diverse array of anatomy and physiology of the pancreas merits their own individual chapters, within their own textbooks. It is imperative to understand the essentials of pancreatic anatomy and physiology in order to contemplate pancreatic pathology and the circumstances that lead to transplantation. This chapter will explain the anatomy and physiology of the pancreas on a gross and histological level. We will describe the pancreatic blood supply, venous drainage, and the organ's anatomical relationships and how they interplay with normal pancreatic function. Awareness of the embryological development of the pancreas aids in conceptualizing anatomical relationships and potential pathology. The endocrine and exocrine functions of the pancreas will be discussed in detail. These features play a role in pancreas pathology leading to transplantation as well as the surgical anatomy involved with the procedure itself. This chapter is but a small piece of the numerous concepts required for effective comprehension of contemporary pancreas transplantation.

Gross Anatomy

The pancreas is a retroperitoneal organ lying posterior to the stomach and anterior to the first lumbar vertebrae. It weighs roughly 100 g and is 14–20 cm in length (Hruban et al. 2007), about the size of half of a hand (Longnecker 2014). In Fig. 1, the organ and its surrounding anatomic relationships are displayed. The pancreas is divided into four anatomical parts: the head, neck, body, and tail. The head sits to the right of midline positioned within the C loop of the duodenum, anterior to the vena cava. The uncinate process, a projection off the inferior aspect of the head of the pancreas, extends behind the superior mesenteric vein (SMV) and anterior to the inferior vena cava sitting adjacent to the superior mesenteric artery (SMA) (Porrett 2010). The neck is a short segment that overlies the SMV and portal vein. The body and tail extend across the midline superior to the fourth portion of the duodenum forming the floor of the lesser sac. The tail extends into the hilum of the spleen. The intricate anatomic relationship between the pancreas and the main splanchnic blood vessels pose a challenge to the pancreatic surgeon. In the setting of pancreatic neoplasms, these vessels can be invaded, rendering surgery difficult at best or contraindicated at worst.

Embryology

During the fourth week of gestation, two endodermal tissues, the dorsal and ventral pancreatic buds, come together to form the pancreas. They are derived from pancreatic epithelial stem cells and give rise to the exocrine and endocrine cell lines. The dorsal bud is larger and forms the superior head, neck, body, and tail of the gland. The ventral bud develops as part of the hepatic diverticulum in communication with the biliary tree and migrates dorsally as the foregut and duodenum rotate in a clockwise fashion between the fourth and eighth week of development. Both develop from the primitive duodenal endoderm. Congenital abnormalities can lead to a variety of anatomical abnormalities and will be discussed later in this chapter. Normally, the ventral bud will form the uncinate process and the inferior portion of the head of the pancreas. The full development of acinar tissue extends into the postnatal period (Longnecker 2014).

The main duct, also known as the duct of Wirsung, is formed as the distal portion of the dorsal bud duct and ventral bud duct fuse in the

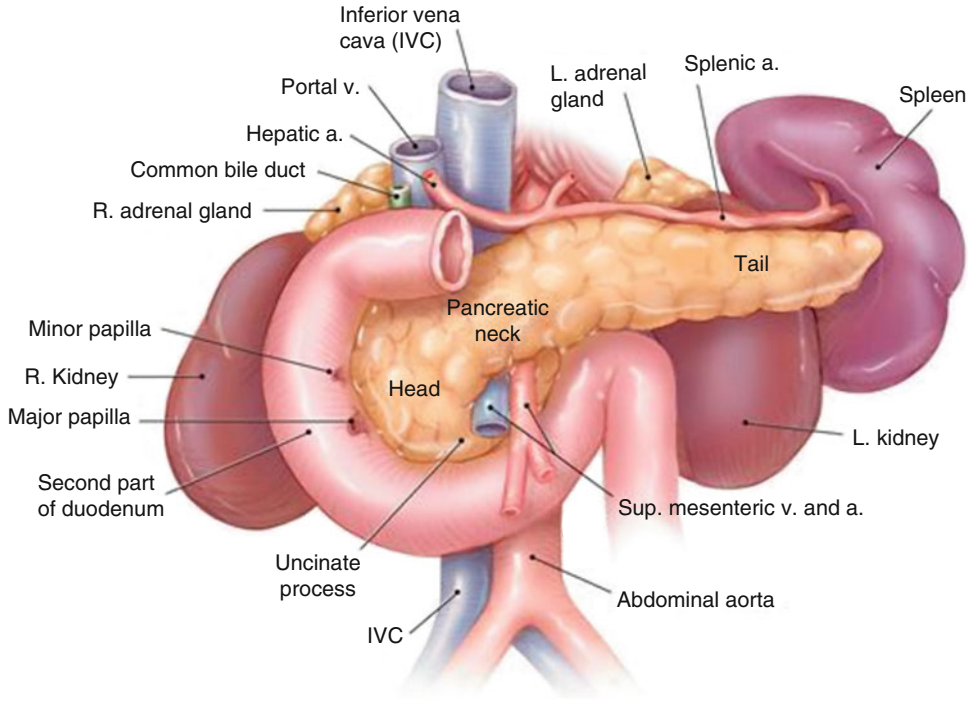

Fig. 1 Anatomic relationships of the pancreas with surrounding structures. (Image by Jennifer Parsons Brumbaugh used with permission of the publisher)

eighth week of gestation. The duct of Wirsung typically joins the common bile duct and enters the second portion of the duodenum at the major papilla. Anatomically, the aperture where biliary and enzymatic fluids enter the duodenum is known as the Ampulla of Vater and is surrounded by the Sphincter of Oddi. Just distal to this marks the embryologic transition between foregut and midgut. An accessory duct, the duct of Santorini, develops from the proximal portion of the dorsal bud duct. The accessory duct can be functional or nonfunctional. Also, it may directly communicate with the main pancreatic duct or may drain into the duodenum separately, via the minor papilla.

Abnormalities of fusion between the ventral and dorsal pancreatic ducts can result in pancreas divisum. Here, the dorsal duct drains the majority of pancreatic exocrine secretions into the duodenum via the minor duodenal papilla. The ventral pancreatic duct enters the duodenum via the major duodenal papilla, yet drains only the minority of pancreatic exocrine secretions (Sabiston and Townsend 2012). This abnormal drainage can lead to obstructed or refluxed pancreatic secretions, which frequently leads to a clinical presentation of pancreatitis.

On a microscopic level, the exocrine secretions are formed in the acinar tissues of the pancreas. The enzymatic effluent drains from an acinus into intralobular duct, which will course through pancreatic lobules. These ducts then lead to interlobular ducts which course between lobules. Eventually, the extensive network of intralobular and interlobular ducts drain into the main or accessory ducts (Longnecker 2014). The integrity of this ductal system is essential as leakage of enzymatic secretions can be damaging to surrounding tissue. Small perturbations in exocrine flow can lead to infiltration of effluent into the interstitial space of the pancreas. The local tissue damage manifests as pancreatitis, which can have varying phenotypic presentations from minor pain and inflammation to widespread pancreatic necrosis.

Other developmental anomalies in pancreatic gland formation exist. Annular pancreas is a result

of aberrant migration of the ventral pancreas bud. Here, pancreatic tissue can wrap circumferentially around the second portion of the duodenum (Sabiston and Townsend 2012). If tight enough, it can form a proximal gastrointestinal obstruction and require bypass with a duodenojejunostomy. Annular pancreas can exist on its own, or can be associated with other congenital defects including Down syndrome, malrotation, intestinal atresia, and cardiac malformations. Though not exactly anomalous, ectopic pancreatic tissue can arise anywhere along the primitive foregut. They are most frequently encountered in the stomach and duodenum. Along with gastric tissue, heterotopic pancreatic tissue may also be found in a Meckel's diverticulum (Sabiston and Townsend 2012). The caustic secretions from this tissue can cause ulceration of surrounding small bowel, becoming a more esoteric cause of gastrointestinal tract hemorrhage.

Initiation of pancreatic development is influenced by a number of molecular factors and pathways that influence its organogenesis. Of these, PDX1 (pancreatic duodenal homeobox 1), PTF1 (pancreas-specific transcription factor 1), notch-signaling pathway, critical to duct and acinar formation and exocrine differentiation, hedgehog signaling pathway, and Wnt signaling pathway have been found to be most critical. In PDX1 mouse knockouts, the pancreas never develops (Sabiston and Townsend 2012). 95% of acinar cells express PTF1, and in null mice, acini do not form. Though these proteins are key in pancreatic development, their exact roles and interactions are yet to be elucidated. It is the hope that these complex protein signaling pathways can one day be a target for pharmaceutical development.

Arterial Blood Supply

The arterial blood supply to the pancreas is a complex network of redundant vasculature cascading from the celiac trunk and SMA. Both of these blood vessels are solitary aortic branches displayed prominently in Figs. 2a, b. These arteries have branch extensively to provide splanchnic inflow and provide a rich collateral network around the pancreas (Longnecker 2014). Specifically, four named vessels provide the bulk of blood flow to the head of the pancreas. The anterior and posterior superior pancreaticoduodenal arteries arise from the gastroduodenal artery (GDA) and within the pancreas. They collateralize with the anterior and posterior inferior pancreaticoduodenal arteries, which arise from the SMA, prior to the first jejunal arterial branches. During pancreas procurement, it is important to preserve the vessels (Cameron and Cameron 2017). In the setting of small bowel procurement or liver with a replaced right hepatic artery, careful attention has to be given to the point of transection of the SMA. A pancreatic graft can still be procured for transplantation in these settings, but it is prudent to keep the inferior pancreaticoduodenal arteries in continuity with enough SMA to safely attach an iliac Y graft (to be discussed in later chapters). Likewise, a replaced right hepatic artery may arise from the SMA more proximally than the pancreaticoduodenal arteries. In this setting, the hepatic allograft can be isolated along with proximal SMA and a carrel patch of aorta while preserving the pancreas for transplantation. The neck, body, and tail receive arterial inflow from branches of the splenic artery and left gastroepiploic artery. The dorsal pancreatic artery, originating from the splenic artery, runs posterior to the body and becomes the inferior pancreatic artery supplying the body and tail. The greater pancreatic artery, of pancreatic magna, is the largest vessel supplying the pancreas from the splenic artery. It has a rare incidence of hemorrhage in the setting of pancreatitis, a complication which can be fatal. In general, the arterial supply is quite redundant, making the pancreas a richly vascular organ.

Venous Drainage

The venous drainage of the pancreas parallels the arterial system, although it drains into the portal system, rather than systemic circulation. The anterior and posterior inferior pancreaticoduodenal

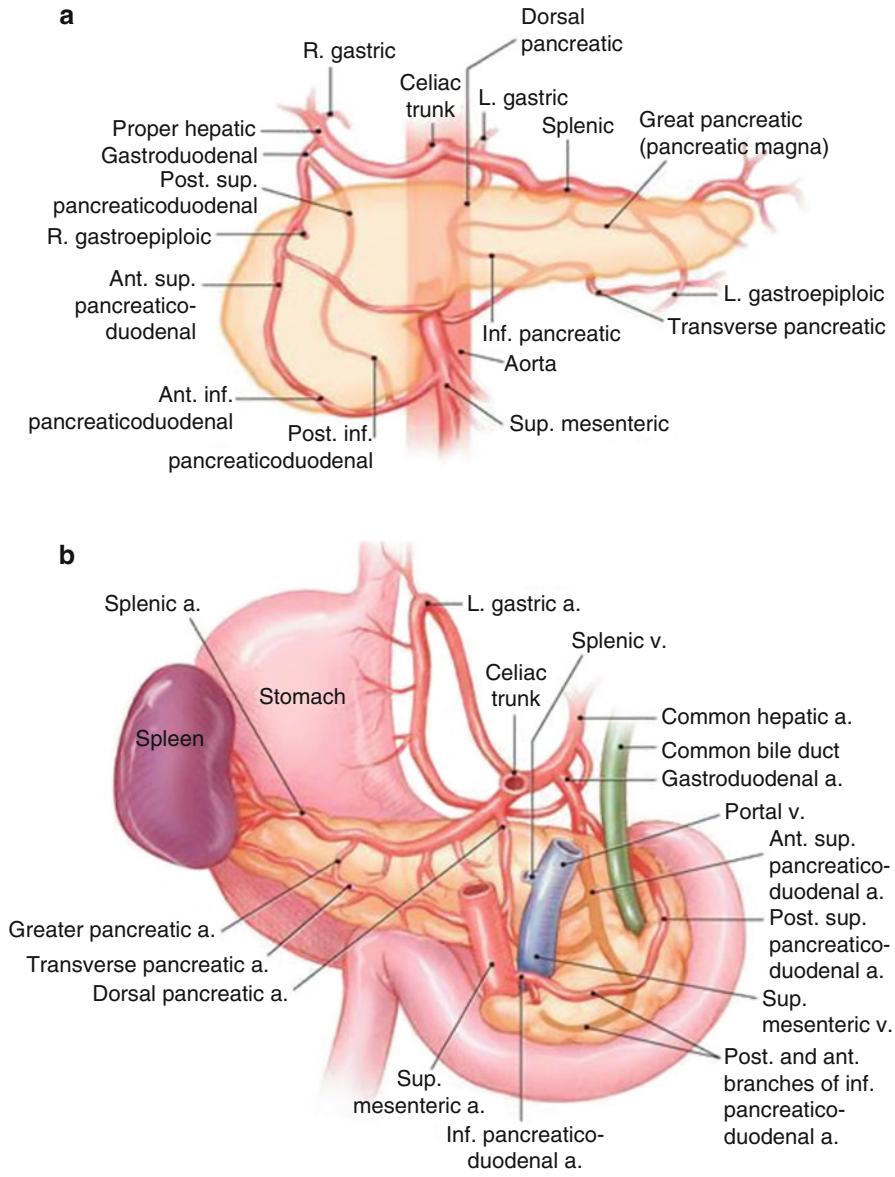

Fig. 2 Arterial blood supply of the pancreas from the front (**a**) and back (**b**). (Image by Jennifer Parsons Brumbaugh used with permission of the publisher)

veins drain the head of the gland. They then follow to the SMV at the superolateral border of the pancreatic neck. The anterior and posterior inferior pancreaticoduodenal veins drain most frequently into the right gastroepiploic vein prior to its confluence with the SMV at the inferior border of the pancreas. The venous drainage network can be somewhat variable, but eventually all venous drainage eventually enters the portal vein, formed posterior to the neck of the pancreas at the confluence of the splenic and superior mesenteric veins. During pancreas procurement, it is important to find a point on portal vein division that is amenable to the liver and pancreas transplant teams (the portal vein is an important source of hepatic allograft inflow and the only source of pancreatic

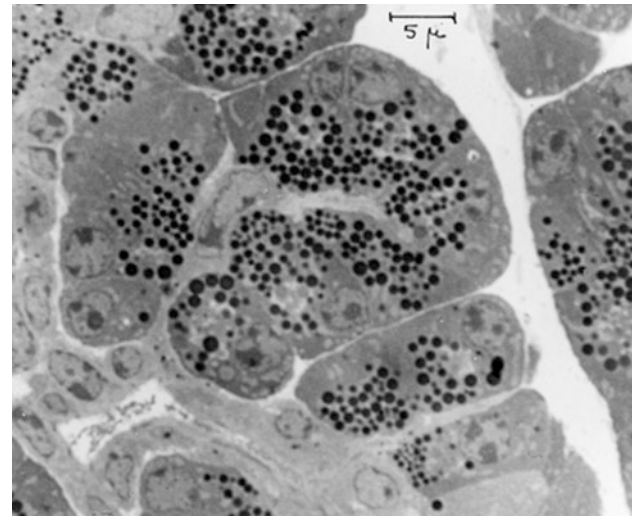

Fig. 3 Acinar and centroacinar cells under low power electron micrograph. (Attribution to Fred Gorelick; created by James Jamieson)

allograft outflow). There is individual variation in the location of the lymph nodes surrounding the pancreas although there are assigned lymph node station numbers that correspond to a relative anatomical location. However, these numbers are not often used in Western publications (Longnecker 2014).

Physiology

Exocrine Pancreas

The exocrine pancreas is a complex tubular network. It produces digestive enzymes (proteases) and bicarbonate-rich fluid providing the necessary components to aid in digestion. The acinar cells, which can be seen in Fig. 3, compose 85% of the pancreas and produce enzymes that digest proteins including trypsin, chymotrypsin, carboxypeptidase, and elastase. They are arranged in a complex intertwined tubular network (Longnecker 2014). Proteases are produced in inactive forms and stored as intracellular zymogen granules (Fig. 3). In the duodenum, enterokinase is produced which in turn activates trypsin from trypsinogen. Trypsin then further propagates proenzyme activation, leading to digestion. Pancreatic amylase and lipase are produced in their active forms hydrolyzing polysaccharides into oligosaccharides and fats into free fatty acids, respectively (Porrett 2010).

Ductal cells secrete bicarbonate-rich fluid under the influence of both vagal and humoral control. This provides the medium to deliver digestive enzymes to the gut and allows for the optimal basic pH for enzyme function. The content of pancreatic fluid can change based on the state of the pancreas. At low secretory rates, the concentrations of chloride and bicarbonate ions are similar to that found in normal plasma. With stimulation however, the concentration of bicarbonate increases dramatically while chloride decreases. In the current understanding of this mechanism, extracellular CO_2 diffuses across the basolateral side of the ductal cells. Inside the pancreatic duct cells, intracellular carbonic anhydrase hydrates the CO_2 to form HCO_3- and H+. Furthermore, an anion exchanger on the apical membrane of the pancreatic duct cells secretes intracellular HCO_3- into the pancreatic duct lumen for Cl−. The H+ byproduct is exchanged for a Na+ on the basolateral side of the pancreatic duct cell in order to maintain physiologic intracellular pH. Na+, K+ -ATPases provide the Na+ gradient that allows for HCO_3- secretion.

Pancreatic secretion occurs in different phases. In the cephalic phase, the pancreas is stimulated by vagal input in response to the sight, smell, or taste of food. This stimulation induces the

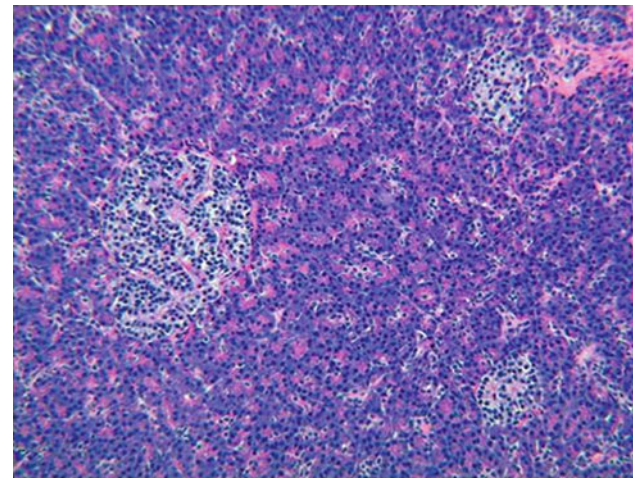

Fig. 4 Human pancreas with three islet cells. (Attribution to Dr. Daniel Longnecker MD)

secretion of pancreatic enzymes from acinar cells. In the gastric phase, vagal reflexes initiated by gastric distention yield additional acinar cell secretion of pancreatic enzymes. During the intestinal phase, acidification of the duodenal lumen causes the release of secretin from S cells. Once activated, secretin receptors cause an increase in cyclic adenosine monophosphate (cAMP) and activate the HCO_3-, Cl− exchanger, as well as increase the activity of carbonic anhydrase and excretion of H+. Lipids, proteins, and carbohydrates cause the secretion of cholecystokinin (CCK) once inside the duodenum, the main mediator of pancreatic enzyme secretion.

Endocrine Pancreas

In normal physiology, pancreatic exocrine function is extremely important. To the transplant surgeon however, pancreatic exocrine secretions need to be excreted. The surgical methods to eliminate pancreatic enzymes have long been the bane of pancreas transplantation. The endocrine pancreas is comprised of islet (islets of Langerhans) cells derived from the foregut endoderm and can be seen in Fig. 4. Islets can vary in size, the majority of which are between 50 um and 100 um in diameter (Hellman 1959). In humans, the number of islets is calculated to be between 500,000 and one million with the highest density in the tail of the pancreas. The acinar and islet cells differentiate from endodermal cells found in the embryonic buds. The main goal of the endocrine pancreas is to regulate the body's energy utilization, namely, carbohydrate metabolism.

Insulin is synthesized in the pancreatic beta cells comprising roughly 75–80% of the pancreas. Beta cell formation occurs before birth with additional proliferation through the second year of life. As plasma glucose levels increase, beta cell stimulation allows for proinsulin, the precursor for insulin, to synthesize and eventually cleave into insulin and residual C-peptide. Both are released directly into the bloodstream in equal amounts. In addition to glucose, a number of hormonal factors directly influence insulin release including gastric inhibitory peptide, glucagon, CCK, amino acids, and free fatty acids. Inhibitors of insulin secretion include somatostatin, amylin, leptin, and pancreastatin. Vagal and beta sympathetic stimulation augment insulin secretion, while alpha sympathetic stimulation inhibits insulin secretion.

Glucagon, secreted from alpha cells comprising 15% of the pancreas, functions to elevate blood glucose levels. Alpha cells appear in 3-week old embryos and organized islets appear at 10 weeks (Sabiston and Townsend 2012). Glucagon effectively stimulates glycogenolysis and gluconeogenesis in the liver. Glucagon is under tight hormonal and neural control and acts primarily in a reciprocal fashion to insulin in order to maintain glucose concentration in the blood.

Somatostatin, stimulated by acid in the duodenum, is secreted by delta cells comprising 5% of the cells of the pancreas and has profound inhibitory effects on the gastrointestinal tract. Somatostatin has been shown to inhibit the release of insulin, glucagon, and pancreatic polypeptide in addition to overall gastric, pancreatic, and biliary secretion. Synthetic versions of somatostatin are routinely used to treat many endocrine and exocrine disorders of the pancreas and gastrointestinal tract. Pancreatic polypeptide is secreted by F-cells under vagal control are considered the fourth most prevalent endocrine cell type. Most are derived from the ventral embryologic structures, ultimately the uncinate process. It decreases gallbladder and pancreatic secretion. Other peptides including VIP, amylin, galanin, and serotonin are secreted by pancreatic islets and have diverse roles. Other influencers on glucose homeostasis include an array of enteric peptide hormones released from the proximal gastrointestinal tract.

Anatomy of the Transplanted Pancreas

Significant effort is placed into the back table preparation of the transplanted pancreas. Proper arterial inflow and outflow are vital to graft viability, as the most common reason for early graft loss is thrombosis. As discussed earlier, the pancreatic allograft receives a dual blood supply from splenic artery, primarily supplying the body and tail of the gland, and superior mesenteric artery, primarily supplying the head and neck. There is extensive intrapancreatic vascular collateralization, allowing redundancy of arterial blood supply. A donor iliac Y-graft is used to reconstruct the superior mesenteric and splenic arteries, allowing a single recipient arterial anastomosis to be constructed at the time of implantation (Cameron and Cameron 2017). The specific surgical technique involved with pancreas transplantation will be discussed in this text.

Outflow of the pancreatic allograft is through the portal vein, which can be anastomosed to systemic circulation (iliac veins or vena cava) or splanchnic circulation (portal vein or SMV). Many transplant surgeons elect to use an iliac venous conduit to lengthen a foreshortened portal vein. Other surgeons are concerned the redundant portal vein may increase the thrombotic risk.

The duodenal C loop allows for proper excretion of pancreatic exocrine secretions. During the donor operation, the pylorus and segments 1–4 of the pancreatic graft are preserved. Remembering that the gastroduodenal artery is often sacrificed as part of the concurrent liver procurement, during the back table preparation of the graft, much of the duodenum is resected to eliminate sections that may have poor vascular supply. The final graft should contain a duodenal segment only large enough to contain the Ampulla of Vater and allow safe anastomosis formation. If used, a staple line along the duodenal conduit is often imbricated to reinforce this relatively ischemic segment of duodenum. Some surgeons elect to respect the entire duodenal segment entirely, performing instead a pancreatic ductal anastomosis. As will be discussed in a later chapter, there are many different strategies to allow for excretion of pancreatic enzymes.

Pancreas Transplant Physiology

Diabetes mellitus has its nomenclature rooted in Greek and Latin, literally meaning “sweet urine.” The disease represents a disorder of glucose metabolism, which leads to chronic hyperglycemia. Type 1 diabetes is the result of autoimmune or idiopathic beta cell destruction that ultimately leads to insulin deficiency. Evidence now suggests that this autoimmunity results from an imbalance between aggressive and regulatory T cell subsets (Orban et al. 2010). Type 2 diabetes is primarily a disease of insulin resistance and may be associated with varying degrees of beta cell dysfunction. Other less common causes of hypoinsulinemia include pancreatitis, trauma, or pancreatectomy.

Diabetes is a debilitating chronic disease, which leads to both macroangiopathies and microangiopathies. Macroangiopathic complications include coronary artery disease, cerebrovascular disease, and peripheral vascular

disease. Microangiopathic complications include retinopathy, peripheral neuropathy, and nephropathy leading to end-stage renal disease. Type 2 diabetics are typically initially treated with a prescription of lifestyle modification. Dietary changes along with an improved exercise regimen can improve insulin receptiveness alone. Many patients, however, will require oral medical therapy and some may need further insulin therapy to maintain euglycemia. Costs due to hospital admissions from diabetic complications are a significant burden to the healthcare system and the patient. Despite what a patient may perceive as euglycemia when they check glucose levels, daily fluctuations can still cause complications like blindness, renal failure, stroke, and heart attack. To avoid fluctuations, continuous glucose monitors may be more durable in second-to-second glucose monitoring. When properly treated, this may limit complications. Still though, life expectancy is significantly reduced and quality of life worsens as diabetes progresses.

Medical therapy of diabetes is constantly evolving and improving. The medical armamentarium to treat diabetes now includes rapid and long-acting insulin analogs, biguanides, gliptins, glitazones, and A-glucosidase inhibitors. An "artificial pancreas" system is currently available. Here, a continuous glucose monitors measures interstitial fluid glucose via a subcutaneous sensor and relays information to a monitor. This is then linked with an insulin pump, allowing a "closed loop" system to maintain tighter glycemic control without direct patient dosing.

For patients with difficult to manage type 1 diabetes who do not respond appropriately to conventional and conservative approaches to blood glucose management, whole pancreas transplantation is a treatment option. Allogenic islet transplantation is a less invasive approach; however, islet engraftment remains less durable than whole gland transplantation. Long-term insulin independence has remained inconsistent. As reported by the Collaborative Islet Transplant Registry, 70% of patients achieve insulin independence within their first year, but that number drops to 35% by year three.

While the ultimate goal of pancreas transplantation is independence from exogenous insulin therapy, in the face of advancing medical therapy, transplant rates have declined. Despite this, graft survival has improved to approximately 14 years (Lombardo et al. 2017). Today, pancreas transplantation is most commonly indicated in uremic Type 1 diabetic patients along with kidney transplantation. Less commonly, it is being performed either as a pancreas transplant alone or for Type 2 diabetes.

When successful, recipients of pancreatic allografts immediately return to normal fasting and postprandial glucose levels. Eventually, hemoglobin A1c levels return to normal levels. As reported by The International Pancreas Transplant Registry, 1-year graft survival rates have improved to 85% for SPK (simultaneous pancreas-kidney) transplants, 78% for pancreas after kidney transplants, and 76% for pancreas only transplants.

With decreases in morbidity and mortality, those patients who eventually become insulin independent report a better quality of life. In type 1 diabetics, for example, glucose-induced insulin secretion is restored thereby normalizing fasting glucose levels. Additionally, hypoglycemia-induced glucagon secretion and hepatic glucose production is restored as well (Barrou et al. 1994). Patients with long-standing autonomic neuropathy have been reported to have improved epinephrine response and normalization of hypoglycemia symptom recognition after pancreatic transplantation (Kendall et al. 1997). There is also a reported stabilization of their diabetic sequela. Retinopathy, nephropathy, neuropathy, and microvascular and macrovascular diseases associated with poor glucose control have been seen to improve after transplantation.

Conclusion

The value of pancreatic transplantation in the appropriate candidate cannot be understated. The anatomical and physiological concepts of the pancreas are paramount to understanding pancreatic pathology and successful transplantation. From this chapter and the others within this text, we

intend for the reader to have a well-balanced comprehension of the key concepts in contemporary pancreatic transplantation.

Cross-References

- Autologous Islet Cell Transplant
- Follow-Up Care of the Pancreas Transplant Recipient
- Medical Benefits of Pancreas Transplantation
- Medical Evaluation of the Diabetic Patient for Pancreas Transplant
- Surgical Complications of Pancreas Transplant
- Surgical Technique of Pancreas Transplantation
- UNOS Perspective on Pancreas Transplantation

Acknowledgments We express our gratitude to the contributing authors who granted us access to their photographs for reproduction in this chapter:
1. Gorelick and Jamieson (2005), Fig. 3.
2. Hruban et al. (2007), Figs. 1 and 2a, b.
3. Longnecker (2014), Fig. 4.

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Modern Parenteral Nutrition

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Contents

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Abstract

Intestinal failure (IF) is the inability of the gastrointestinal tract to absorb energy, vitamins, minerals, electrolytes, and fluids. Patients with IF would need nutrition support in the form of nutritional supplements, tube feeding, or *parenteral nutrition* (PN). Duration of nutrition support depends on severity of IF. Complications of long-term PN make it a less favorable treatment; small bowel transplant is done to avoid these complications. Although small bowel transplant is not for every patient with IF, early referral and evaluation are highly recommended. This chapter will discuss the use of long-term or home PN in patients with IF who would require small bowel transplant. After the right patient is selected for long-term PN, the PN formula is adjusted to meet the requirements of the patient, and the patient is evaluated by social workers, case managers, and trained nurses for PN. After discharge from the hospital, the patient is monitored closely for complications.

Keywords

Parenteral nutrition · Home parenteral nutrition · Cycled parenteral nutrition · Nutrition-focused physical assessment · Malnutrition · Parenteral nutrition failure · Intestinal failure · Intestinal transplantation · Intestinal rehabilitation

Introduction

With the advancements of medical technology, we see more patients who survive catastrophic abdominal emergencies and/or trauma leading to short bowel syndrome and IF. The use of home or long-term PN is growing. Patients with IF who are dependent on PN should be evaluated for small bowel transplant to avoid complications of long-term PN. Placing the patient on long-term or home PN is a complex process that involves a multidisciplinary team of physicians, nurses, case managers, social workers, pharmacists, and homecare agencies. Thorough psychosocial and living condition evaluations should be done on every patient going on home PN.

Intestinal Failure and Indications for PN

PN is the intravenous provision of fluid and nutrients, including dextrose, proteins, lipids, vitamins, electrolytes, and trace elements, and is the primary medical treatment for chronic IF. PN was pioneered in the 1940s, and by the 1970s patients were able to be successfully managed long term in the home setting. IF was defined by Fleming and Remington in 1981 as "a reduction in the functioning gut mass below the minimal amount necessary for adequate digestion and absorption of nutrients" (Fleming and Remington 1981). There are three types of IF, which are outlined in Table 1 (Dibb et al. 2013).

PN should be initiated in patients with a nonfunctioning or inaccessible gastrointestinal (GI) tract only when it is estimated to be needed for at least 7 days in order for its benefit to outweigh the associated risks. PN initiation can be delayed for up to 7 days in well-nourished patients if enteral or oral nutrition is expected to be started within this timeframe (McClave et al. 2016). In more extreme cases, PN will be required in order to maintain

Table 1 Types of intestinal failure

Type of intestinal failure	Description
Type 1	Common, temporary, post-abdominal surgery, requires short-term fluid or nutritional support during recovery
Type 2	Less common, postsurgical resection, associated with metabolic or septic complications, requires longer-term nutrition support for recovery, may develop into type 3 if poorly managed
Type 3	Rare, chronic, requires long-term or home parenteral nutrition support; may also be treated with intestinal lengthening procedures or intestinal transplant

Dibb et al. (2013)

Table 2 Indications for PN

Indication for PN	Underlying condition
Obstruction	Paralytic ileus, volvulus, tumors, adhesions
Dysmotility	Scleroderma, amyloidosis, pseudo-obstructions
Malabsorption	Crohn's disease, radiation enteritis, high output enterostomy, fistulae, mesenteric ischemia
Congenital defect	Atresia, familial adenomatous polyposis, postural orthostatic tachycardia syndrome
Short bowel syndrome	Extensive resections

O'Keefe et al. (2006); Gotthardt et al. (2013)

fluid, nutrient, and electrolyte balance (O'Keefe et al. 2006). Indications for PN and some of their possible underlying conditions are outlined in Table 2. The most commonly seen indication for home PN is short bowel syndrome with the most common underlying conditions being ischemia and Crohn's disease (Gotthardt et al. 2013).

Evaluation of Patient for PN

Initiation of PN, as with all medical treatments, does not come without risks. Therefore, it is imperative to complete a comprehensive assessment of each patient to determine if it is appropriate for PN in the home setting. This most often begins in the hospital. Assessment should be approached as a multidisciplinary effort including physicians, dietitians, nursing, social work, and case management, often designated as a nutrition support team (NST). There are many benefits to a multidisciplinary team approach. It has been shown that nutrition support teams lead to improved clinical outcomes, fewer complications, and improved care and cost savings (Saalwachter et al. 2004). Each discipline's roles and responsibilities for PN management are outlined below.

A thorough comprehensive assessment should be completed prior to initiating PN. The assessment should include a review of the medical, surgical, and nutrition history. This will determine the nutrition status of the patient including the presence of malnutrition. A review of the patient's medical history should include information on the chief complaint, present and past illnesses specifically relating to indications of IF, and the presence of renal, heart, and liver diseases and diabetes mellitus. Patient medications should be reviewed for any that may alter absorption, antibiotics, and vitamin/mineral or herbal supplements. Anthropometric measurements are reviewed for changes in weight. The patient and family members, if present, should be interviewed and asked questions on medical/surgical history, nutrition history, and social history, if home PN is indicated (Table 3). Social/psychosocial assessment may reveal concerns that may impact the ability for the patient to safely administer PN in the home setting.

Nutrition-focused physical assessment should follow the patient interview (White et al. 2012). A nutrition-focused physical assessment can reveal information regarding nutrition status that may not be identified from the interview or review of medical records. The exam should assess weight loss, energy intake, and functional ability and include a head to toe examination of the body for fat and muscle mass and fluid status. In addition, each area of the body should be examined for signs/symptoms of micronutrient deficiencies. Traditional examination techniques of inspection,

Table 3 Patient assessment questions for PN initiation

Medical/surgical history
Has the patient had any GI altering surgeries?
What is the patient's remaining bowel length?
Are there any stomas, fistulas, drains, or tubes present?
Any change in bowel habits? Diarrhea, constipation?
Does the patient have increased metabolic needs due to sepsis, trauma, fistulas or abscesses, open wounds, or chronic diseases?
Is the patient experiencing other GI symptoms, i.e., nausea or vomiting?
Nutrition history
What is the patient's usual body weight?
Has there been a significant weight gain or loss from the usual body weight? Over how long did this occur?
Has the patient experienced a change in eating habits? Over how long?
Has the patient experienced a decrease in functional status?
Does the patient take a vitamin or mineral supplement?
What is the relationship between oral intake and bowel habits? How soon after eating does the patient have a bowel movement or ostomy output?
Are there food or medications present in output?
Social history
What is the patient's housing situation?
Does the patient live alone or with family members?
Is the patient employed?
What type of insurance does the patient have?
Does the patient have any history of chemical dependency?
Does the patient suffer from altered mental status?

palpation, percussion, and auscultation should be utilized (White et al. 2012). A thorough review will guide the treatment plan and potentially identify factors that may result in complications with initiation of nutrition support.

Initiating PN from the Outpatient Clinic

Occasionally, a patient may be referred to an outpatient physician for evaluation for PN. In this case, the patient would be evaluated in an office visit by a physician and registered dietitian (RD) to determine the presence and severity of malnutrition, the degree of metabolic stress, the patient's ability to take and to tolerate oral or enteral nutrition, and/or the expected length of time before oral or enteral nutrition may be resumed. If PN is deemed appropriate and necessary, the patient should be admitted to the hospital for close monitoring.

Line Placement

PN can be administered as a peripheral or central solution. Peripheral PN (PPN) is reserved for short-term use (10–14 days). To prevent phlebitis, PPN is formulated as a 3-in-1 solution (dextrose, amino acids, and lipids) with an osmolarity $\leq$900 mmols/L (Boullata et al. 2014). Despite the provision of all three macronutrients, PPN does not usually meet caloric requirements in hypermetabolic and fluid restricted patients. Therefore, placement of a central catheter is recommended.

Central PN infusion requires a central venous access device (CVAD). A CVAD is a device with its tip in the superior vena cava (SVC) near the junction of the right atrium for safe administration (Ayers et al. 2014). Due to the high osmolarity of PN, this position is necessary for the high blood flow rate (Steiger 2006). Central PN can be delivered via a temporary central venous catheter (CVC), peripherally inserted central catheter (PICC), tunneled catheters (Hickman, Hohn, Groshong, and Broviac), and implanted venous access device (porta catheter).

To determine the appropriate central catheter, the anticipated length of therapy should be established, either short term ($\leq$1 month) or long term (>1 month). Non-tunneled catheters such as PICCs and CVCs are appropriate for short-term PN. CVCs are appropriate for inpatient use only. A PICC is a semipermanent catheter that is inserted via the antecubital veins (i.e., basilica, brachial, and cephalic) with the tip terminating in the mid to lower SVC (Ayers et al. 2014). A PICC is appropriate for both inpatient and home use. Both PICC and CVC tip placements must be confirmed via chest radiograph or fluoroscopy. Advantages of the PICC and CVC are low cost of placement and ease of removal. Disadvantages include higher rate of infection and increased risk of thromboembolism (Paauw et al. 2008). Additionally, a PICC is more difficult to care for in the home setting. The PICC requires additional

tubing as an extension for PN administration, or the patient must have a caregiver administer. Dressing changes must always be completed by a caregiver or home health nurse as it is not feasible to complete with one hand. Therefore, tunneled catheters are the recommended access for long-term home PN use.

Tunneled catheters include Hickman, Hohn, Groshong, and Broviac. Each of these catheters is placed radiologically using local anesthetic and IV sedation. Hickman, Groshong, and Broviac catheters are equipped with a Dacron velour cuff that is used to adhere the catheter to the tissue surrounding the tunnel effectively securing the catheter. Hohn catheters are available with or without cuffs. Sutures are placed at the exit site for approximately 4–6 weeks until the subcutaneous cuff adheres to the tissue; at that time the sutures can be removed. Advantages of tunneled catheters include decreased risk of dislodgement and infection and ease of self-care (Maki and Crnich 2003). The use of an ethanol lock for these catheters has been shown to decrease incidence of infection (Opilla et al. 2007). The *ethanol lock* can only be used in silicone catheters (Hickman, Groshong and Broviac). The lock should be instilled into each lumen of the catheter daily after PN infusion to dwell until the next infusion. Hohn catheters are polyurethane and therefore cannot utilize ethanol as a lock. Implanted ports are long-term devices that are implanted into a subcutaneous pocket, usually in the chest. Ports are ideal for patients requiring intermittent intravenous fluids (IVF) due to the need to access via inserting a non-coring needle through the skin into the septum of the port. Ports can be either silicone or polyurethane.

Multidisciplinary Approach to PN Initiation

The NST will collaborate to initiate PN after the appropriate CVAD is obtained. The physician is responsible for an initial assessment of the patient and approval for initiating PN. Physicians are responsible for ordering the PN formula as well as any laboratory studies required for monitoring including daily blood work (basic metabolic panel, complete blood count, magnesium, phosphorus, hepatic panel). Physicians collaborate with the RD to interpret laboratory studies and caloric/protein needs to formulate individualized PN. Laboratory values should be monitored daily, specifically phosphorus, magnesium, potassium, and glucose for signs of refeeding syndrome. Patients at risk for refeeding syndrome should be identified based on their degree of malnutrition. Abnormal electrolyte values should be repleted prior to initiation of PN (Solomon and Kirby 1990).

An RD completes a nutrition-focused physical exam to determine the patient's degree of malnutrition. The patient's degree of malnutrition along with their age, gender, current weight, goal weight, body composition, and activity level is used to determine calorie, protein, and fluid needs. Indirect calorimetry is the gold standard to determine energy requirements; however at most institutions this is not readily available, and predictive equations are used (Choban et al. 1997). The RD establishes the patient's goal weight and determines the need for weight gain or loss and adjusts the calorie needs accordingly.

Protein requirements are determined using age, weight, nutrition status, and clinical status. Metabolically stressed patients undergoing transplant require 1.5–2.0 gm/kg body weight of protein (Hasse 2001).

Fluid needs can be determined by various equations. Patients requiring PN often have complex fluid losses via high output enterostomies or venting gastrostomies. Total fluid requirements for these patients should be determined by review of intakes and output records, weights, lab values, and vital signs. If PN is the major IV therapy, the volume must cover losses from stomas, fistulas, drains, tubes, diarrhea, and emesis, in addition to urine output and insensible losses (500 mL). Serum levels of sodium, BUN, creatinine, hematocrit, and albumin and monitoring weight can assess the presence of hypovolemia (A.S.P.E.N. 2015).

PN is initiated as either a 2-in-1 solution (dextrose and amino acids) or a 3-in-1 solution. Three-in-one solutions are most often used with patients with poor glucose control or for short-term

peripheral PN in which goal calories cannot be met without lipids. A 2-in-1 solution is preferred due to decreased lipid infusion (see section "PN Complications"). Lipid emulsions can be given as an IV piggyback during the hospital stay.

After initiation of PN, patients are assessed daily to determine tolerance to PN. Vitals, blood work, and intake and output records should be reviewed by the physician and the RD. Electrolytes, including potassium, magnesium, and phosphorus, glucose, and BUN/ creatinine should be measured daily until PN composition is stable (Ayers et al. 2014). A daily physical exam is completed to assess GI function, fluid tolerance, and the integrity of the vascular device.

PN calories, electrolytes, and fluid volume are adjusted daily. Calories should be increased slowly toward goal over time once electrolytes and blood glucose levels are stable (Solomon and Kirby 1990). Physicians should review and approve each formula. The pharmacist evaluates daily PN orders, reviews for compatibility, and acts as a final review prior to compounding. Any questions or concerns are discussed with the RD or physician prior to compounding (Ayers et al. 2014).

Preparing for Home Parenteral Nutrition

Patients requiring PN beyond hospitalization undergo preparation for home PN. The estimated length of therapy and the suspected end point of care are determined. Consults for case management, social work, and NST nurses are placed. Once the PN formula has reached goal calories and has demonstrated stability, it can be cycled (Table 4). Cycling is a process of administering PN over a shortened amount of time. Cycled PN can be infused from 8 to 20 h. This provides a period of infusion-free time for the patient. Cycling has both physiological and psychological benefits for the patient. Physiologically, the rest between infusion times is beneficial for the prevention of PN-associated liver disease (see section "PN Complications"). Cycling can occur in a stepwise method of decreasing infusion time from 24 to 12 h in increments of four to 6 h usually over a period of 2–3 days (Ayers et al. 2014). PN can be safely cycled from 24 to 12 h in 1 day in patients without congestive heart failure, end-stage liver disease, pulmonary dysfunction, or chronic renal failure (Austhof et al. 2015). Hyperglycemia, rebound hypoglycemia, and fluid overload are three possible complications of cyclic PN (Ayers et al. 2014). Tapering is a technique in which the infusion rate is slowly increased and decreased to the goal rate to improve glucose control (Ayers et al. 2014). Tapers most frequently are used for the first hour ("tapering up") and last hour ("tapering down") of the infusion.

Providing PN in the home setting is complex; therefore, the nutrition support nurse must determine an appropriate caregiver, which may or may not be the patient receiving PN, and complete an evaluation of the patient or caregiver to assess their ability to safely follow procedures for PN management. The nurse also provides training which includes catheter care, PN hookup and disconnect, and home monitoring (Table 5). In addition, the nurse collaborates with the case manager and social

Table 4 Conditions for PN stability

Capillary blood glucose <200 mg/dL
No severe electrolyte or acid-base abnormalities
Vital signs stable and unchanged
No dyspnea or tachypnea (>20 breaths/min)

Table 5 Home PN monitoring for patient/caregiver

Intake and output records
Intake
Oral
Enteral
Intravenous
Output
Urine
Drains
Ostomies, fistulas
Signs/symptoms of infection
Temperature ≥ 38 °C
Shaking/chills
Night sweats
Glucose monitoring
Urine dipsticks with morning urine
Peripheral blood glucose monitoring
Daily weights

work to determine home safety. A social worker evaluates the patient's level of function, ability to cope, family support, and reviews pertinent psychological history including a history of mental disorders, depression, or chemical dependency. The social worker may refer to psychiatry for further evaluation if warranted. If the patient does not have support and is unable to safely provide PN at home, a skilled nursing facility will be chosen with the help of the case manager. The case manager is responsible for verifying insurance benefits and supplies needed. Home PN is a costly therapy; therefore, insurance coverage varies depending on the type of program the individual policy offers. Before discharge, the patient will need to be accepted by both the infusion pharmacy and home health nursing with a start of care for the night of discharge.

PN Complications

Although PN can be a lifesaving treatment, it is not without risks and possible complications. Examples of short- and long-term complications of PN are outlined in Table 6.

Refeeding Syndrome

Refeeding syndrome consists of drastic fluid and electrolyte shifts that occur in severely malnourished patients when nutrition is reinstated. Patients at high risk are those who have experienced severe weight loss and starvation, including those with anorexia nervosa, chronic alcoholism, and cancer cachexia, among others. When carbohydrate is reintroduced as the primary energy source, insulin production increases causing a rapid uptake of glucose, fluid, and electrolytes into the cells, which results in the classic symptoms of hypophosphatemia, hypokalemia, hypomagnesemia, and fluid retention. Patients at risk of refeeding syndrome should be identified before PN is initiated in order to prevent its occurrence. Patients should be hemodynamically stable and electrolyte abnormalities corrected before initiating nutrition support and advanced slowly under close monitoring (Solomon and Kirby 1990).

Table 6 Complications of PN

Short-term complications of PN	Long-term complications of PN
Refeeding syndrome	Metabolic bone disease
Fluid imbalance	PN-associated liver disease
Electrolyte abnormalities	Vitamin and mineral deficiencies
Glucose abnormalities	Essential fatty acid deficiency
Catheter malposition	Trace element abnormalities
Catheter-related infection	Recurrent catheter-related infections
Catheter occlusion/ thrombosis	Impaired quality of life

Dibb et al. (2013); Pironi et al. (2006)

Fluid Imbalance

Fluid imbalance and dehydration are common complications among patients with malabsorption. This can be managed with monitoring of daily intake and output records in order to identify increased GI losses (vomiting/diarrhea), decreased urine output, as well as weight changes. Signs and symptoms of dehydration include abrupt fall of body weight, poor skin turgor, tachycardia, headaches, dizziness, muscle cramping in extremities, thirst, dry mucous membranes, urine output <1 L/day, dark urine, and elevated BUN and creatinine. Home PN patients should have additional IVF (liter bags of 0.45% or 0.9% normal saline) on hand to use as needed in addition to PN (Konrad et al. 2012). PN volume can be adjusted in order to prevent further episodes of dehydration.

Electrolyte Abnormalities

Electrolyte abnormalities can be caused by fluid imbalance, excessive intakes or losses, intracellular shifts, or certain medications. Adjusting the PN formulation can correct mild abnormalities, but critical electrolyte levels should be treated emergently (Whitmire 2003).

Glucose Abnormalities

Glucose abnormalities are the most common metabolic complication of PN administration. Hyperglycemia can occur even in patients without a history of diabetes and may be due to acute illness, steroid use, excessive dextrose administration, or rarely chromium deficiency. To prevent hyperglycemia, dextrose load should be low during initiation of PN and advanced gradually while monitoring blood glucose levels regularly. PN-induced hyperglycemia may be treated by adding regular insulin to the PN formula, usually at an initial dose of 0.05–0.1 units per gram of dextrose. Hypoglycemia may result from excessive insulin in the PN and should be treated by discontinuing the PN infusion and immediately starting a dextrose containing fluid infusion. Rebound hypoglycemia may occur upon abrupt stopping of the PN and can be prevented by tapering the infusion rate by 50% for 1 or 2 h prior to discontinuation (Ayers et al. 2014).

Noninfectious Catheter Complications

Catheter complications are a major problem for home PN patients and are one of the key causes of PN failure which would indicate intestinal transplantation (Pironi et al. 2006). Catheters can become dislodged as a result of being inadequately secured, improper dressing change techniques, or physical activity. Catheter tips can migrate as a result of changes in intrathoracic venous pressure. Dislodgement risk can be minimized with the use of sutures and tunneled catheter cuffs, as well as proper catheter care training for patients and caregivers (Dibb et al. 2013). Catheter malposition may present as change in external catheter length, lack of blood return, sluggish flow, edema, or discomfort of the chest, neck, or accessed extremity. If catheter malposition is suspected, the line should be evaluated and may need to be replaced. Catheter occlusions can be caused by fibrin formation, lipid deposits, or medication precipitation. Fibrin occlusions may resolve with administration of tissue plasminogen activator, while lipid occlusions can be treated with ethanol lock and saline flushes. There is not enough evidence to support the use of prophylactic anticoagulation therapy in home PN patients to prevent thrombotic events. The routine use of heparin flushes may be association with increased infection risks and other long-term complications such as heparin-induced thrombocytopenia; therefore only saline flushes are currently recommended (Dibb et al. 2013). If catheter thrombosis occurs and is untreated, it may result in the need to remove the catheter and loss of the access site (Huisman-de Waal et al. 2011). Complete catheter fracture is rare but would require removal of all parts of the catheter (Dibb et al. 2013).

Infectious Catheter Complications

Catheter-related infections (CRIs) are common and serious complications on PN infusions. Increased risk of bloodstream infections has been associated with implanted ports when compared to tunneled catheters, multi-lumen catheters, use of home PN catheters for non-PN medications, improper catheter hub disinfection, infusion of lipids more than twice weekly, and frequent blood drawing from the catheter. Other factors affecting infection risks include patient's use of alcohol and tobacco, income and education level, cultural factors, underlying disease, anatomy, and training in catheter care. The most common causes of catheter-related infections are hub contamination and migration of skin flora at the insertion site. Although less common, hematogenous seeding from a source of infection and contamination of the infusate are other causes of CRI. Infections that develop in implanted ports are often more difficult to treat than those in tunneled catheters and generally require removal of the device. Therefore, if long-term PN use is expected, a single-lumen tunneled catheter should be recommended, that will be used exclusively for PN infusion, with intravenous lipid provision limited to once or twice weekly, if possible. Meticulous adherence to catheter care protocols can mitigate the risks of catheter-related infections (Buchman et al. 2014).

Treatment of catheter-related infections should aim to salvage the device whenever possible, as

frequent line exchanges can lead to loss of venous access. Exit site infections can usually be managed with oral antibiotic therapy. Tunnel infections require line removal and line replacement at an alternate site. If catheter-related sepsis is suspected, use of the line should cease and antibiotic therapy started, as central blood culture results are pending. Of course, if the patient is severely ill with catheter sepsis or signs of shock are present, the line should be removed (Dibb et al. 2013). A new central venous access device can be placed when repeat blood cultures are negative for 48 h. Patients who experience recurrent CRIs may benefit from use of antibiotic or ethanol locks, which should be instilled daily into each lumen of the catheter after PN infusion is completed and dwell for several hours. Ethanol lock is preferred over antibiotic lock for long-term use due to the risk of developing antibiotic resistance (Opilla et al. 2007).

Quality of Life

Catheter-related complications and the hospital readmissions that they require are associated with decreased quality of life. The threat of catheter-related complications has been linked to feelings of fear, anxiety, fatigue, depression, and social impairment in home PN patients, which have a large impact on their quality of life. Patients may experience lack of adequate sleep, if PN infusions are done overnight, due to frequent urination or noise from the infusion pump. Independence and social interactions have been shown to be diminished in home PN patients due to the presence of a catheter, PN infusion schedule, mobility, and physical complaints (Huisman-de Waal et al. 2011). Quality of life is also affected by age, length, and frequency of PN infusions, amount of oral intake, presence of a stoma, and narcotic usage (Dibb et al. 2013).

Metabolic Bone Disease

Studies have shown that metabolic bone diseases such as osteoporosis and osteomalacia are common among home PN patients. Potential contributing factors could include aluminum toxicity, calcium, phosphate, or vitamin D imbalances, chronic inflammation, and corticosteroid use. Relevant lifestyle risk factors include smoking and alcohol use and a sedentary lifestyle. Patients with an underlying condition of inflammatory bowel disease are at higher risk as they tend to require home PN for longer periods of time, and more frequently receive corticosteroid therapy, and therefore should be closely monitored to prevent complications of low bone mineral density. Presence and severity of bone disease are diagnosed from bone mineral density measurements, which should be regularly monitored in patients on long-term home PN (Pironi et al. 2002). Monitoring can be done with the use of dual x-ray absorptiometry (DXA) scan which should be performed every 2 years. Measurements are done of the lumbar spine and proximal femur. Patients who are diagnosed with osteopenia or osteoporosis (T-scores: −1 to −2.5, or −2.5 or lower, respectively) are placed on oral calcium and vitamin D in addition to what is provided to PN. Bisphosphonates given IV may also be prescribed.

Vitamin, Trace Element, and Essential Fatty Acid Deficiencies

Patients receiving PN should be provided with daily multivitamins and trace elements. Levels should be routinely monitored with lab tests and physical assessment of signs of abnormalities; and identified deficiencies should be repleted. Essential fatty acid deficiency should also be regularly evaluated for using the lab value of an elevated triene-tetraene ratio, as well as assessment of physical symptoms, and may be treated with adjustment in intravenous lipid dose or with supplemental oral or topical oil administration (Dibiasse-Fortin 2003).

Liver Disease

Hepatic dysfunction is common in patients receiving long-term PN and presents with abnormal liver functions tests and intrahepatic cholestasis

and may progress into PN-associated liver disease if untreated. Risk factors for development of liver function abnormalities include small bowel length less than 100 cm and higher total caloric intake from PN than estimated needs, hepatotoxic medication use, prolonged bowel rest, episodes of sepsis, and bacterial overgrowth (Luman and Shaffer 2002). Development of *PN-associated liver disease* may also be affected by manganese and aluminum toxicities or deficiencies of carnitine, choline, and essential fatty acids. Provision of lipids in excess of one gram per kilogram per day is associated with cholestatic complications (Gotthardt et al. 2013). Steatosis is a common occurrence during PN initiation, usually associated with mildly elevated transaminases that resolve after several weeks. Occasionally, steatosis leads to steatohepatitis in those on long-term PN. Development of end-stage liver disease is rare (Luman and Shaffer 2002). Risk of developing PN-associated liver disease increases with length of time on PN (Cavicchi et al. 2000). Standard soy bean-based lipid emulsions contain large amounts of omega-6 polyunsaturated fatty acids which have been associated with a pro-inflammatory response and impaired biliary secretions; recent evidence suggests that the use of alternatives such as fish oil-based emulsions may be more protective (Xu and Li 2012). Liver function abnormalities in PN patients should be addressed by determining and treating non-PN causes, adjusting PN formulation, and encouraging enteral intake. It is important to evaluate a patient for intestinal transplant prior to the development of end-stage liver disease as the outcomes of isolated intestinal transplantation are better than those of combined liver and intestinal transplants (Gotthardt et al. 2013).

PN Failure

Indications for intestinal transplant include PN failure, which may occur due to development of life-threatening PN-associated complications or when there is a high risk of death or greatly reduced quality of life due to the underlying disease. Home PN failure-associated indications for intestinal transplant may include impending or evident liver disease, recurrent incidents of catheter-related sepsis, catheter-related thrombosis of multiple central veins, loss of venous access, or recurrent episodes of severe dehydration (Pironi et al. 2006; Gotthardt et al. 2013).

Mortality

Despite the numerous potential complications of home PN, the primary causes of death for these patients remain their underlying disease, including cancer, scleroderma, or amyloidosis. Home PN patients with the underlying disease of inflammatory bowel are most often succumbing by unrelated conditions such as secondary cancer or heart disease. Deaths directly related to home PN therapy are rare, with the most common being catheter-related sepsis (Scolapio et al. 1999).

Monitoring Parenteral Nutrition Prior to Intestinal Transplantation

PN has been the standard of care for those with IF. Unfortunately, it is not without severe, life-threatening complications. Intestinal transplantation is a viable option for those with irreversible IF and PN failure (Hashimoto et al. 2015). Until lifesaving organs are available, it is important to carefully monitor the patient on PN to optimize surgical outcomes. The goals are to improve and maintain nutrition parameters, protect hepatic and renal function, and prevent the occurrence of infections (Matarese et al. 2007).

Nutrition Parameters

A complete nutrition-focused physical assessment (White et al. 2012) by the RD is required prior to surgery. Most individuals with intestinal failure are underweight (BMI < 18.5 kg/m^2) (Bizari et al. 2014). A weight goal should be determined and PN calorie requirements adjusted to promote weight gain (Table 7), but overfeeding should be avoided. Although rare, patients who are overweight (BMI 25–29.9 kg/m^2) or obese (BMI > 30 kg/m^2) should have their calories reduced in PN to achieve a healthier weight.

Table 7 Estimated calorie needs based on body mass index

BMI (kg/m^2)	Estimated calorie needs (kcals/kg)
<18.5	35–45
18.5–24.9	25–35
25.0–29.9	20–25
>30.0–34.9	15–20
>35.0	10–15

Vitamins/Minerals

Thiamine, vitamin B12, fat-soluble vitamins, selenium, copper, and zinc are the most common deficiencies to occur in short bowel syndrome, especially if more than 60–100 cm of terminal ileum is resected (Scolapio and Ukleja 2005; Nightingale and Woodward 2006; Rannem et al. 1996). Serum vitamins, trace elements, and iron studies should be measured during the transplant evaluation and deficiencies corrected (Table 8). If levels are low, oral or intravenous (IV) supplementation must be started and levels rechecked every 2–3 months to assess efficacy of therapy. In addition to the standard multivitamin infusion, extra thiamine, pyridoxine, ascorbic acid, folic acid, cyanocobalamin, and vitamin K can be supplemented to PN (Table 9; Buchman et al. 2009). However, vitamins A, D, and E need to be given orally. These fat-soluble vitamins are available in oral gel caps and can be pierced and squeezed under the tongue which may aid in better absorption as to swallowing the gel cap whole.

It is important to maintain bone health pre-transplant as corticosteroids prescribed after surgery can increase calcium excretion. A DXA scan should be obtained to assess baseline bone mineral density during the pre-transplant evaluation.

Copper (Braga et al. 2015), selenium (Rannem et al. 1996), and zinc (Scolapio and Ukleja 2005; Wolman et al. 1979) levels are commonly depleted in patients with short bowel syndrome. In addition to the multiple trace element injection, extra individual doses can be added to PN (Refer to Table 9). It is not uncommon for chromium and whole blood manganese levels to be elevated. The standard multiple trace element injection must be removed from PN and the remaining trace elements added back individually.

Table 8 Serum nutritional parameters measured prior to intestinal transplantation

Vitamins	Trace elements	Iron studies
A (retinol)	Zinc	Iron
B1 (thiamine)	Copper	Total iron binding capacity (TIBC)
B6 (pyridoxal phosphate)	Selenium	Ferritin
B12 (cobalamin)	Whole blood manganese	Transferrin saturation
Methylmalonic acid (MMA)	Chromium	
Folic acid		
C (ascorbic acid)		
25-Hydroxyvitamin D		
E (alpha-tocopherol)		

Table 9 Individual dosing of vitamins and minerals in parenteral nutrition (Buchman et al. 2009)

Vitamin/mineral	Additional PN dosing (ranges)
Ascorbic acid	500–1000 mg/mL
Cyanocobalamin	100–1000 mcg/mL
Folic acid	5 mg/mL
Pyridoxine	50–100 mg/mL
Thiamine	100 mg/mL
Vitamin K	2–10 mg/mL
Copper	0.4 mg/mL[a]
Selenium	40 mcg/mL[a]
Zinc	1–5 mg/mL[a]

[a]Increment dosing

Iron deficiency is not prevalent in this population as it is absorbed in the duodenum and proximal jejunum. However, if the patient is strictly nil per os, receiving iron-free PN or taking oral proton pump inhibitors or H2 blockers decreasing gastric acid, iron deficiency may occur. Low-molecular-weight iron dextran can be added to non-lipid PN formulations (Hwa et al. 2016); however, it is not a common practice due to the instability of total nutrient admixtures. The cationic ions of ferric iron can neutralize the anionic ion surface in fats which results in the breakdown of the emulsion (Driscoll 1990). The patient should receive intravenous iron by weekly

injections if serum iron and ferritin levels are depleted and total iron binding capacity is elevated. Iron therapy should not be given during existing infection.

Electrolytes

Electrolytes are absorbed throughout the gastrointestinal tract. In short bowel syndrome, their absorption can be reduced depending on the remaining bowel left in continuity and the absence of the ileocecal valve. The presence of the colon improves absorption of electrolytes (Amiot et al. 2013). Patients with a jejunostomy can lose large amounts of sodium, potassium, and magnesium (Nightingale and Woodward 2006; Nightingale et al. 1990). In addition, bicarbonate losses are increased from ileostomy outputs (A.S.P.E.N. 2015). When determining the dose of electrolytes in PN, it is important to look at urine, stoma, diarrhea, fistula, tubes, and drain outputs to assess the electrolyte content lost. Trends in the serum electrolyte levels can determine further adjustments in PN dosing.

Protecting Hepatic and Renal Function

Preventing overfeeding can help protect hepatic function. Care should be taken not to exceed dextrose and lipid doses in PN which can lead to further hepatic failure. Intravenous lipids containing combinations of soybean oil, MCT oil, olive oil, and fish oil have led to improved liver function compared to fat emulsions with exclusively soybean oil (Dai et al. 2016).

Preventing dehydration can preserve renal function as the patient will receive a number of potentially nephrotoxic drugs after transplantation (Matarese et al. 2007). PN volume must cover all GI losses minus any oral or IV intakes. It is not uncommon for these patients to require 4–4.5 L per day of total PN volume, plus additional IV fluid. The patient should keep daily intake and output records to monitor adequate urine output (1–1.5 L), and other output losses, and record daily weight to allow for accurate adjustments in PN volume. The multidisciplinary team should be contacted by the patient if symptoms of dehydration occur. Although PN is usually cycled at home, PN infusion can be given over longer periods of time to prevent dehydration and damage to the kidneys (Matarese 2010). Antisecretory medication such as the somatostatin analogue, octreotide, can be added to PN. The dose can range from 300–1200 mcg/day.

Monitoring Parenteral Nutrition Post-intestinal Transplantation

During the posttransplant period, rejection, infection, and surgical complications can occur; thus, antirejection and antimicrobial medications are initiated. Surgical stress alters metabolism of cytokine-mediated stimuli resulting in hypoalbuminemia, hyperglycemia, and elevated C-reactive protein levels. Nutritional goals include providing adequate macro- and micronutrients to treat catabolism and promote healing, treating electrolyte abnormalities, and achieving optimal glucose control via PN. Adequate protein should be provided in PN and calories should support presurgical dry weight. Becoming nutritionally independent from PN is the desired outcome.

Fluid Requirements

PN can be initiated within 24–48 h after surgery if the patient is hemodynamically stable and can continue for several weeks until an oral diet is advanced (Matarese 2010). Fluid requirements are reduced significantly in PN from the preoperative prescription. A PN volume of 1–1.5 L daily is not uncommon due to other IV fluids and medications given postoperatively. PN sodium should be adjusted from the preoperative formula due to the reduction in volume. Amino acid concentrations of 15–20% can be used to reduce total volume required for compatibility. PN lipids are held and can be resumed once the patient is off propofol. Close monitoring of renal function, serum sodium, weight, and intake and output records can determine when the PN volume can be increased

Table 10 Nephrotoxic medications post intestinal transplant

Antimicrobials	Immunosuppressive	Corticosteroids
Aminoglycosides	Tacrolimus	Hydrocortisone
Amphotericin B		Methylprednisolone
Colistimethate		Prednisone
Ganciclovir		
Foscarnet		

to 1.5–2 L. Minimum PN volume should remain until the patient is weaned off.

Immunosuppression

Medications to prevent rejection begin immediately after transplantation and are nephrotoxic (Table 10). Tacrolimus and corticosteroids aid in adaptation of the new transplanted organ(s) and antimicrobials prevent infection (Hashimoto et al. 2015). Due to nephrotoxicity, trends of rising electrolyte levels (potassium, phosphorus) should be monitored daily and reduced in PN to maintain normal plasma levels. However, potassium and calcium levels may decline by increased excretion from corticosteroids. In addition, corticosteroids increase protein catabolism and cause sodium and fluid retention (Burt et al. 2007). Reduced magnesium and chloride levels and higher CO_2 have been seen in posttransplant patients (O'Keefe et al. 2007). Replacement doses can be administered intravenously and modest doses added back to PN. Large single increases should be avoided due to risk of overcorrecting. Close monitoring of daily serum levels is imperative.

Both tacrolimus and corticosteroids can cause insulin resistance leading to hyperglycemia. Regular insulin can be added to PN and adjusted based on blood glucose monitoring and as these medication doses are modified.

Weaning Off PN

Once the stoma begins working and the nasogastric suction tube is removed, a clear liquid diet can begin. Based on the patient's tolerance, the diet can be advanced to softer solid foods. Patients should be advised to eat slowly and consume small, frequent meals. PN can be weaned once the patient is tolerating $\geq$50% of an oral solid diet (Ramisch et al. 2016) by first reducing dextrose kcals and removing weekly lipid infusions. Most patients begin weaning off PN around 3 weeks to 2 months posttransplant (O'Keefe et al. 2007; Ramisch et al. 2016). Complete weaning was reported by one center in 30.8 $\pm$ 25 days (Matarese et al. 2009). Some institutions start enteral feedings via jejunostomy or nasogastric tubes to bridge between PN and oral diet.

Vitamin and mineral levels should be monitored posttransplant. Increases in riboflavin (vitamin B2), pantothenic acid (vitamin B5), and pyridoxine (vitamin B6) were reported in ileostomy effluent during rejection (Girlanda et al. 2012). In another report, serum pyridoxal 5′ phosphate (vitamin B6) was deficient in intestinal and multivisceral transplant patients despite continuation of PN therapy which resolved after prompt IV and oral intervention (Matarese et al. 2009).

Complications Requiring Resumption of PN

Occasionally, patients may need to resume PN after being weaned off in the event of acute cellular rejection, anastomosis dehiscence, or chylous leak. Two biomarkers that may guide nutritional intervention following intestinal transplantation are insulin-like growth factor-1 and calprotectin. Normal levels of these biomarkers indicate the patient is nutritionally replete without the need for PN. During episodes of malnutrition, insulin-like growth factor-1 is decreased and calprotectin levels increased, indicating that PN should continue or be restarted (Vrakas et al. 2015).

Monitoring Patient for Intestinal Rehabilitation

Intestinal rehabilitation is the process of optimizing bowel function through diet modification, pharmacological therapy, and surgical intervention to aid in nutritional autonomy and independence from PN. A modified diet, restricting simple sugars and increasing complex carbohydrates, soluble fiber, and salt, aids in increased intestinal absorption. Hypotonic and hypertonic fluids should be avoided and instead small quantities of an oral rehydration solution (glucose-saline mixture, 90 mmol/L sodium) (Nightingale and Woodward 2006) sipped between meals throughout the day.

Antidiarrheal medications, given 30 min before meals and bedtime, such as loperamide, diphenoxylate HCL-atropine sulfate, codeine sulfate, and tincture of opium, aid in reducing intestinal motility and stooling by decreasing fluid and sodium loss. Antisecretory medications such as H2 blockers and proton pump inhibitors are used to suppress gastric acid and have shown to reduce jejunostomy output and improve nutrient absorption (Cortot et al. 1979). Pancreatic enzymes can be used to aid in digestion. In patients with short bowel as well as the colon in continuity, a bile acid sequestrate can be given, such as cholestyramine or colestipol, which bind bile acids that can be irritating to the colonic lining. Antimicrobials can be given to treat small intestinal bacterial overgrowth, and probiotics can be beneficial in preventing it. Trophic substances, such as growth hormone and glucagon-like peptide-2 (teduglutide [rDNA origin]), can also be approved in select patients. *Teduglutide* has shown to increase mucosal growth, reduce intestinal losses, and promote intestinal absorption (Jeppesen et al. 2001). Close monitoring prior to and during therapy is required. Baseline amylase, lipase, C-reactive protein, prealbumin, and citrulline levels and a colonoscopy are obtained prior to starting therapy. The patient must keep intake/output records for 2 weeks before therapy begins to determine baseline urine output and weight. Once stoma or diarrhea output is under control and weight and electrolytes are stable, IV fluids or PN can be decreased or weaned.

Surgical measures by autologous reconstruction and bowel lengthening are viable procedures for selected patients to be nutritionally autonomous from PN together with diet and pharmacological therapy (Abu Elmagd 2015). When intestinal rehabilitation fails with the presence of PN failure, intestinal transplant should be considered.

Conclusion

Home PN and small bowel transplant are acceptable treatments for IF. Patients should be evaluated thoroughly before considering either treatment. Home PN should be done by trained healthcare providers. It should be managed by a multidisciplinary team of healthcare providers in a specialized center.

Cross-References

- Central Line Management and Intestinal Failure
- Nutrition Considerations in Multivisceral Transplantation
- Recent Evolution of Gut Rehabilitation
- Visceral Transplantation: Current Trends and Long-Term Outcome

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Central Line Management and Intestinal Failure

Colette Shaw

Contents

Abstract

Intestinal failure (IF) arises when the gut function is below the minimum required for absorption of macronutrients, water, and electrolytes, and intravenous supplementation is needed to maintain homeostasis. Central venous access (CVA) is required in both acute and chronic forms of the condition. The preservation of venous access and the management of catheter-related complications are important determinants of long-term survival in those who suffer chronic intestinal failure. For optimal CVA outcomes, patients should be managed at IF centers

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of excellence by multidisciplinary teams that include interventional radiologists. CVA management should include evidence-based protocols implemented by trained staff and close monitoring of outcomes to ensure safety and efficacy.

Keywords
Central venous access · Central venous catheter · Intestinal transplantation · Intestinal failure · Parenteral nutrition · Catheter-related bloodstream infection · Catheter-related thrombosis

Introduction

Intestinal failure (IF) arises when the absorptive capacity of the gut is insufficient to meet the nutritional requirements of the patient and dependence on intravenous supplements ensue. Prior to the advent of parenteral nutrition (PN) in the 1960s, the prognosis for those suffering from IF was dismal (Wilmore 1972). PN via central venous access (CVA) is now the mainstay of care in those with chronic forms of the condition. Catheter-related complications including thrombosis and infection can lead to loss of access with potentially devastating consequences for these patients. The objectives of this chapter are to guide the reader through the management of CVA in this patient population including device selection, the optimal site for access, tips for troubleshooting, and steps to prevent and treat catheter-related complications.

What Is Intestinal Failure?

The pathophysiology of IF is described by five conditions: short bowel, intestinal fistula, intestinal dysmotility, mechanical obstruction, and extensive small bowel mucosal disease (Pironi et al. 2015). The mechanisms that underlie these conditions include malabsorption, restricted oral/enteral intake, loss of fluids and electrolytes, small bowel bacterial overgrowth, hypophagia, increased gastrointestinal transit time, and increased metabolic demands. A functional classification of IF based on onset, metabolic criteria, and expected outcomes has been described (Table 1; Shaffer 2002). Type 1 (acute IF) typically manifests after major abdominal surgery and/or in the critically ill patient. The condition is self-limiting, resolving over days to weeks (Gardiner 2011). Type II is a prolonged acute condition, often in metabolically unstable patients. Occasionally it may occur as an acute exacerbation of chronic IF (Type III). These patients often require multidisciplinary care in a high dependency or intensive care unit. Intravenous supplementation is required over a period of

Table 1 Intestinal failure functional classification

Type	Onset	Example	Level of care	Duration	Prognosis
I	Acute	Ileus following laparotomy	Surgical floor	Days to weeks	Self-limiting
II	Acute on chronic or prolonged acute	Mesenteric ischemia necessitating laparotomy and extensive enterectomy	HDU/ICU	Weeks to months	Up to13% inpatient mortality 50% prolonged PN 40% full intestinal rehabilitation
III	Chronic	Stable patient with short bowel syndrome	Home or long-term care facility	Months to years	20–50% CIF reversed and weaned off home PN after 1–2 years 5-year survival 80% adults and 90% children in CIF due to benign disease

HDU high dependency unit, *ICU* intensive care unit, *PN* parenteral nutrition, *CIF* chronic intestinal failure (Schaffer 2002)

weeks to months. In-hospital mortality up to 13% has been reported in this group (Pironi et al. 2015). Approximately 40% achieve full intestinal rehabilitation, while another 50% require long-term enteral tube nutrition or progress to chronic IF requiring home PN. Type III describes chronic IF and may evolve following type II acute IF. It may also be the result of progressive gastrointestinal or systemic benign diseases, congenital digestive diseases, or the end stage of intra-abdominal or pelvic malignancies. Short bowel syndrome, a form of IF that is defined by <200 cm of residual bowel, is the commonest cause of chronic IF due to benign disease and accounts for over 50% of cases in children and over 75% in adults in Europe (Pironi et al. 2006).

The management of these patients, particularly type II, is complex. Patients in need of long-term PN support should be enrolled in a multidisciplinary intestinal rehabilitation program as early as possible. Once metabolically stable, many patients and/or their caregivers can be trained to manage PN at home. About two-thirds of patients with chronic IF are partially or totally rehabilitated back into society (Baxter et al. 2006; Winkler 2005). The 5-year survival for those with chronic IF due to benign disease is now reported at about 80% in adults and 90% in children (Pironi et al. 2012). Intestinal transplantation is reserved for cases where PN fails, the mortality risk from the underlying disease is high, the patient has IF with high morbidity, or low acceptance of PN (Pironi et al. 2012; Beath et al. 2008; Fishbein 2009).

CVA

The initiation and maintenance of CVA requires input from a multidisciplinary intestinal rehabilitation team including an interventional radiologist, a surgeon, the patient and/or their caregiver (Schneider 2006; Carreira Villamor et al. 1997). While safety and efficacy data now support the use of PN as the primary treatment in those with chronic IF (Pironi et al. 2012; Beath et al. 2008; Fishbein 2009), long-term CVA and parenteral feeding are associated with potentially serious catheter-related and metabolic complications, e.g., catheter-related sepsis, vascular thrombosis, IF-associated liver injury.

CVA Device Selection

The ideal CVA device should be radiopaque, biocompatible, and durable. The catheter and the vein in which it is placed should allow brisk infusion and easy aspiration of fluids. The patient's clinical status, the type, frequency and duration of therapy, the patient's history of CVA and patency of the access veins, patient preference, and operator experience all need to be considered when selecting the device and the access site.

Duration of Therapy

Short-term (1–3 weeks) central venous catheters (CVC) are nontunneled (temporary), 20–30 cm long catheters inserted into a central vein (subclavian, internal jugular, innominate, axillary, or femoral vein). They may have a single or multiple lumens and range in size from 5–14 French. They are designed for continuous, short-term (1–3 weeks) infusions; drug delivery, hemodialysis, apheresis, and central venous pressure monitoring. Such catheters are indicated in those with acute IF or acute on chronic exacerbations of IF in whom there are multiple indications for short-term venous access. They are routinely used in patients in the Intensive Care Unit (ICU). More permanent access can be considered once the patient has been stabilized and the acute phase issues have been resolved.

Intermediate (<3 months) CVCs are usually nontunneled devices specifically designed for prolonged intermittent use; they include peripherally inserted central catheters (PICC) and Hohn (Bard Access Systems, Salt Lake City, UT) catheters. PICCs are nontunneled, central catheters inserted through a peripheral vein of the arm. They range from 2–7 French and may have one, two, or three lumens. The catheter extends from the puncture site to the superior vena cava (SVC). Hohn catheters may be tunneled or nontunneled, single, double, or

triple lumen, up to 42 cm total length, centrally inserted catheters. The catheter is made of silicone and has a nontapered tip. Both PICCs and Hohn catheters can be used for prolonged continuous or intermittent infusion therapies (up to 3 months) both in hospitalized patients and in outpatients.

Long-term (>3 months) CVCs include tunneled CVCs or a totally implanted port. Tunneled catheters travel through a short subcutaneous tunnel before entry into an accessed vein. Sizes range from 3.5 to 21F. The cuff induces an inflammatory reaction within the subcutaneous tunnel, leading to fibrosis and consequent catheter fixation, usually within 3–4 weeks after insertion. The cuff also inhibits migration of organisms into the catheter tract, thus reducing infection rates compared with temporary catheters. Totally implanted ports consist of a reservoir connected to a CVC, which may or may not be valved. The reservoir is implanted in the chest or arm. Ports have lower reported rates of catheter-related bloodstream infections than both tunneled and nontunneled CVCs (Leonidou and Gogos 2010). Tunneled CVC is recommended for patients requiring continuous access, while a totally implantable access device should be reserved for patients who require long-term, intermittent vascular access. Either device may be considered for patients maintained on home PN. Arteriovenous fistulae have also been used for long-term PN, but while this access is associated with very low rates of infection, occlusion rates are relatively higher than other forms of CVA (Versleijen et al. 2009).

In general, the smallest diameter catheter and minimum number of lumens should be used to minimize the risk of catheter-related complications (Dezfulian et al. 2003; Knutstad et al. 2003). Multilumen catheters may be used when multiple simultaneous therapies are required or when infusion of noncompatible medications and fluids require additional venous access. In patients with chest ports who require higher infusion rates, the flow through a catheter 6F or greater will be limited by the size of the accessing Huber needle used and not the catheter lumen. In patients receiving PN, there is insufficient evidence to recommend that a single lumen be dedicated exclusively to that purpose (O'Grady et al. 2011b).

Materials

Almost all CVCs are now made of silicone or polyurethane. These materials have been associated with fewer infections than polyvinyl chloride or polyethylene (Maki and Ringer 1987; Sheth et al. 1983). Silicone, a soft biocompatible rubber, is one of the least traumatic and thrombogenic materials available. Silicone catheters are more prone to compression and "pinch off." Polyurethane, on the other hand, is a tougher and stiffer material. Greater catheter stiffness and size are associated with an increased risk of mechanical phlebitis. In general, silicone is more compatible with infusates. Polyurethane is more susceptible to degradation by various drug solvents (Crnich et al. 2005).

In an attempt to reduce catheter-related complications, catheters and cuffs that are coated or impregnated with antimicrobial, antiseptic, or antithrombotic agents have been developed. The data available relates primarily to triple-lumen, temporary catheters in adult patients with catheter dwell time < 30 days. Two meta-analyses of first-generation catheters coated externally with chlorhexidine/silver showed a reduced risk for catheter-related bloodstream infection (CRBSI) compared with standard noncoated catheters (Mermel 2000; Veenstra et al. 1999). Three prospective, randomized studies of second-generation catheters demonstrated a significant reduction in catheter colonization but were underpowered to show a difference in CRBSI (Brun-Buisson et al. 2004; Ostendorf et al. 2005). In 2011, the US Centers for Disease Control and Prevention (CDC) recommended the use of a chlorhexidine/silver sulfadiazine or minocycline/rifampin-impregnated CVC in patients whose catheter is expected to remain in place more than 5 days if, after successful implementation of a comprehensive strategy to reduce rates of catheter line associated bloodstream (CLABSI) infection, the infection rate is not decreasing (O'Grady et al. 2011a).

Thrombolytic coatings (e.g., heparin) have been incorporated into the design of some tunneled catheters. A retrospective comparison of heparin-coated and noncoated hemodialysis catheters showed a significantly lower risk of catheter-related bacteremia among the heparin-coated

catheters but the coating did not decrease the risk of catheter malfunction (Pierce et al. 2000). The longevity of the coatings, the risk of antibiotic resistance, and the safety of the antithrombotic coatings, particularly in patients who may be heparin-induced thrombocytopenia positive need to be assessed. At present, there is inadequate evidence to support the use of PICCs or tunneled catheters coated with anti-infective or antithrombotic drugs.

Indications for Use

Inpatient Acute Care

Nontunneled CVCs are used for short-term CVA in the majority of hospitalized patients. A multicenter study analyzing 2,101 CVCs inserted in critically ill patients showed PICCs were associated with a significantly lower rate of bloodstream infection than standard CVC (Garnacho-Montero et al. 2008). No randomized control study has yet proven this. A meta-analysis from Turcotte et al. (2006) including 48 papers published between 1979 and 2004 did not find clear evidence that PICC is superior to CVC in acute care settings. In this meta-analysis, infectious complications did not significantly differ between PICC and CVC; however, all PICC placements were performed without ultrasound guidance. In relation to PN in hospitalized patients, PICCs should be considered in patients with tracheostomy and in patients where insertion-related complications are increased (e.g., patients with coagulation abnormalities) (Pittiruti et al. 2009).

Hemodialysis

Patients who develop IF may suffer kidney failure in the early acute phase of their illness, during an acute exacerbation of chronic IF, or in the setting of a complication, e.g., catheter-related sepsis. Temporary or permanent hemodialysis access may be required.

Hemodialysis access of <3 weeks duration should be obtained using a noncuffed, or a cuffed, double-lumen percutaneously inserted catheter. Noncuffed femoral catheters should not be left in place longer than 5 days and should be left in place only in bed-bound patients. Tunneled cuffed venous catheters are the method of choice for temporary access of >3 weeks duration. Some patients who have depleted all other access options require permanent access via tunneled cuffed catheters.

The vascular access of choice for maintenance hemodialysis is the native arteriovenous fistula (AVF). The NKF-KDOQI Clinical Practice Guidelines for Vascular Access currently recommends restricting venous access for patients with chronic kidney disease stage 4 or worse (Vascular access work group 2006). For CVA a tunneled catheter inserted into the internal jugular vein is recommended. These devices may include 4, 5, 6, or 7 French single, double, or triple lumen catheters; centrally inserted CVC, 6–10 French single, double, or triple lumen cuffed tunnel catheters; 6–9 French ports. In general, a PICC line should not be placed in patients at risk for future hemodialysis vascular access. For patients who have a primary AVF maturing but need immediate hemodialysis, tunneled cuffed catheters are the access of choice.

Parenteral Nutrition

CVA which allows delivery of nutrients directly into the SVC or the right atrium is needed in most patients who are candidates for PN. It is recommended that peripheral PN delivered via short or midline catheters should be used only for a limited period of time, and only for nutrient solutions with osmolarity of 850 mOsm/L or less (Isaacs et al. 1977). For high osmolarity PN, the tip of the catheter should be placed in the lower third of the SVC or in the upper right atrium to avoid injury to the endothelium of the veins. Both nontunneled CVCs and PICCs are suitable for short-term inpatient PN (Raad et al. 1993; Safdar and Maki 2005). Neither device has been shown to be superior in this patient population. For medium term or home PN (<3 months), PICCs, Hohn catheters, tunneled catheters, and ports are appropriate (Ryder 1995). PICCs may not be suitable for patients receiving home PN who are self-caring as the PICC effectively disables one arm. While medium- and long-term access devices are both acceptable in outpatients, PICCs have been associated with a higher incidence of thrombosis

in patients with hematological malignancies. This is an important consideration in patients who have had previous thromboses and in those who are receiving therapy which may increase the thrombotic tendency. The risk of PICC-related venous thrombosis can be reduced by avoiding PICCs with calibers greater than 4 French and by using ultrasound guidance for placement.

For prolonged use and home PN for greater than 3 months, a tunneled catheter or port is advised (Ryder 2006). In the oncology population, venous ports are associated with lower infection risk; however, these ports are being used intermittently for administration of chemotherapy agents. In patients undergoing PN, daily or continuous access is usually necessary, and the infusant is more favorable for growth of microorganisms. In general, venous ports have been recommended only for patients who require long-term, intermittent vascular access, while for patients requiring long-term frequent or continuous access, a tunneled CVC is preferable. Ports are enclosed and may be more acceptable to younger patients. If the patient or their caregiver is not willing to access the port, PN clinical personnel will need to be available to do so, otherwise an alternative device should be considered.

Site Selection

The risk of catheter-related complications varies according to the site of catheter insertion. Factors to consider when selecting the optimal insertion site include the presence of acute or chronic thrombus in the target vein, CVA history, and integrity of the surrounding soft tissues. If the patient does self-care, the preferred exit site location should be marked preprocedure with the patient standing in order to ensure the exit site is visible and accessible to the patient (Steiger 2002).

Peripheral Veins

CVA via peripheral vein may be preferable in a patient with a tracheostomy, severe anatomical abnormalities of neck and thorax, marked thrombocytopenia, and in patients who require home PN for limited periods of time. In the upper limb, PICCs and subcutaneous arm ports are usually placed via the basilic, brachial, or cephalic veins when image-guidance is employed. The basilic vein is the access vein of choice as it is superficial and is usually the largest vein in the arm. Access via the cephalic vein has a higher incidence of thrombosis. This is due to its smaller size and catheter susceptibility to movement and kinking as it overlies the biceps muscle. Brachial vein access carries a greater risk of injury to the brachial artery and median nerve. Port implantation in brachial veins is associated with easy vascular access and a lower risk of complications at insertion. Kuriakose et al. (2002) reported more frequent thrombogenic complications in arm ports than in chest ports (11.4% vs. 4.8% respectively).

Conventional Central Veins

The site for CVA should be chosen after a careful evaluation of the relative risks and benefits of each. The femoral route is often preferred in emergency or high risk situations (e.g., severe thrombocytopenia and/or coagulopathy), where insertion complications are lower and hemostasis is easier to achieve. In patients in whom the internal jugular and subclavian veins are occluded or otherwise unavailable for puncture, or in the event of SVC obstruction, femoral vein access may also be considered. In 2011, the CDC advised against using femoral vein for CVA in adult patients (O'Grady et al. 2011a). This recommendation was based on studies that demonstrated high femoral catheter colonization rates compared with subclavian and internal jugular sites in adults and, in some studies, higher rates of CRBSI (Goetz et al. 1998; Lorente et al. 2005). Femoral catheters were also associated with a higher risk of deep venous thrombosis (DVT) than internal jugular or subclavian catheters (Merrer et al. 2001; Trottier et al. 1995). Femoral venous access should be avoided in patients with aorto-bifemoral bypass grafts or a femoral-distal bypass graft due to the risk of infection. The femoral vein is relatively contraindicated for PN due to the high

risk of contamination at the groin exit site and the high risk of venous thrombosis. Tunneling onto the anterior abdominal wall can take the exit site out of the groin, thus facilitating access and nursing care. In 2012, a Cochrane review of CVA sites for prevention of thrombosis stenosis and infection reported lower risks of catheter colonization and thrombotic complication attributed to subclavian CVA compared to femoral CVA in short-term catheterizations (Ge et al. 2012). Based on evidence from a number of observational studies in which nontunneled CVCs placed via jugular route were associated with higher colonization rates and/or CRBSI than those inserted into a subclavian vein, the CDC 2011 guidelines recommend placing nontunneled CVCs in adults at subclavian rather than jugular or femoral sites (O'Grady et al. 2011a). This recommendation is supported by recent results from a multicenter randomized trial involving 3027 ICU patients in whom nontunneled CVCs were placed (Parienti et al. 2015). Lower rates of bloodstream infection and symptomatic thrombosis in subclavian vein catheterization compared to jugular-vein or femoral-vein catheterization were reported.

Long-term catheterization data comparing subclavian and internal jugular CVA routes among 401 cancer patients showed similar risks for catheter-related complications (Biffi et al. 2009). Radiologists have used both the subclavian and internal jugular veins for chest port insertion. Using ultrasound guidance, the internal jugular vein is easier to puncture than the subclavian vein and is the vessel of choice for CVA by interventional radiologists. The right internal jugular is preferred to the left because it has a relatively straight course, facilitating catheterization and has a negligible risk of symptomatic central venous stenosis and thrombosis. The incidence of central venous thrombosis and/or stenosis for nontunneled catheters has been reported at 40–50% with the subclavian route versus 0–10% with the right internal jugular route (Mermel 2000). Subclavian vein thrombosis can result in painful arm swelling that may necessitate catheter removal, anticoagulation therapy, and/or thrombolysis. Other disadvantages of subclavian vein access include the higher risk of pneumothorax, catheter fatigue, pinch-off, and possibly fracture due to compression by the costoclavicular ligaments and subclavius muscle.

There is inadequate data relating to non-hemodialysis tunneled catheter placement to recommend a preferred site for access. In relation to long-term hemodialysis catheter placement, the NKF KDOQI guidelines strongly recommend avoidance of the subclavian vein unless no other option exists or unless the ipsilateral extremity can no longer be used for permanent dialysis access (Vascular access work group 2006). The right internal jugular vein is the preferred access site as it has a more direct trajectory to the cavoatrial junction and is associated with a lower risk of complications compared to other insertion sites (McBride et al. 1997). Placement via the left internal jugular vein may jeopardize the venous return from the left arm and rule out future fistula formation on that side. Catheter placement in the left internal jugular vein is associated with inferior blood flow rates and higher rates of stenosis and thrombosis compared with those placed via the right internal jugular vein (Cimochowski et al. 1990). If possible the tunneled catheter should be placed on the contralateral side to a maturing fistula (Vascular Access Work Group 2006).

Unconventional Venous Access

The loss of CVA options in a patient requiring long-term hemodialysis or PN can be life-threatening. Alternative means of obtaining CVA include recanalization of occluded vein segments, use of collateral neck or chest veins, catheter placement in the inferior vena cava via infraumbilical, translumbar, or transhepatic approaches, and right atrial catheter placement via transhepatic venous approach.

Collateral neck or chest wall veins develop in response to chronic central venous narrowing and occlusion. In patients with a well-established collateral network via mediastinal, intercostal, paraspinal, or azygos veins, access via these vessels is unlikely to result in symptomatic central venous obstruction. Procedure-related complication rates are comparable to those via conventional venous access sites (Funaki et al. 2001).

Extrathoracic CVA options include femoral vein and translumbar inferior vena cava. In hemodialysis patients, femoral vein access should not be used without first considering lower extremity fistula formation. Permanent femoral catheters are associated with a higher rate of infection and occlusion, resulting in more frequent interventions for catheter maintenance. Translumbar cava access is technically more challenging and time consuming. Infection rates for tunneled catheters are comparable with chest veins but the risk of catheter malfunction is greater (Lund et al. 1995). Transhepatic CVA is associated with a high risk of catheter malfunction due to constant catheter tip movement with respiration. In a review of 36 transhepatic CV access catheterizations, catheter occlusion was reported at 2.4/100 catheter-days (Stavropoulos et al. 2003).

As a last resort, direct right atrial placement via thoracotomy may be performed.

Catheter Occlusion

In a study of the complications of CVA devices in approximately 50,000 patients undergoing home infusion therapy, the most common complication was loss of patency [50]. CVC lumen occlusion affects up to 25% of CVCs placed and may be partial or complete (Moureau et al. 2002). It is defined as an inability to infuse solutions into or withdraw solutions from a CVA device. The incidence of catheter occlusion in home PN patients is about 0.07 episodes/catheter/year (0.059–0.083) (Howard and Ashley 2003). Causes include drug precipitation and lipid residue, anatomical or mechanical obstructions, and thrombotic occlusion. Anatomical or mechanical obstructions may be due to catheter malposition or dislocation, catheter kinking or fracture, and increased intraluminal pressures. Drug precipitation can occur if the same lumen is used to administer noncompatible drugs and the lumen is not flushed adequately between infusions. Proper flushing technique may also help prevent lipid residue building up inside the catheter lumen.

Thrombotic occlusion is caused by the build-up of fibrin within and/or around the catheter (Jacobs 2003). Catheter-related thrombosis can take a number of different forms: fibrin sheath, intraluminal thrombosis, mural thrombosis. The latter refers to thrombus extending from the catheter into the lumen of a vessel, and leading to partial or total catheter occlusion with or without clinical symptoms. Thrombotic complications of CVA manifest as catheter malfunction and/or symptoms of DVT. The overall incidence of asymptomatic and symptomatic catheter-related DVT has been reported to be between 27% and 66%, and 0.3% and 28.3%, respectively (Verso and Agnelli 2003). Complications of upper extremity venous thrombosis include pulmonary embolus (incidence range 5–14%), DVT recurrence (2–5%), and post-phlebitic syndrome (incidence range 10–28%) (Di Nisio et al. 2010; Elman and Kahn 2006; Martinelli et al. 2004; Monreal et al. 1994; Munoz et al. 2008; Spencer et al. 2007).

Preventive Measures

1. Device type and placement
   (a) Use catheters made from less thrombogenic materials (e.g., silicone, second and third generation polyurethane).
   (b) Use a catheter with the least number of lumens required. The risk of thrombosis increases with the number of catheter lumens used (Merrer et al. 2001).
   (c) Venous thrombosis is less common in catheters inserted from the right side compared to those placed from the left (relative risk 0.39) (Verso et al. 2008). The catheter tip should be placed in the caudal SVC. Catheter tips placed at the cavoatrial junction are associated with a relative risk of DVT of 0.26 compared with the tip placed in the SVC or innominate veins (Bozzetti et al. 1983; Verso et al. 2008).
   (d) A greater vessel length exposed to a catheter appears to increase the risk of thrombosis. Left sided placements are associated with higher incidence of DVT than right-sided catheters (Male et al. 2003; Shingarev et al. 2013). PICCs have a substantially higher risk of thrombotic complications (27.2%) than centrally placed CVCs (9.6%).

(e) Catheters impregnated with antithrombotic substances including heparin-antithrombin III are available but given the lack of long-term data relating to the safety and efficacy of these catheters, there is inadequate evidence to support their use in routine practice.
(f) Ultrasound-guided placement minimizes endothelial damage and reduces the risk of catheter-associated thrombosis at the puncture site. Two meta-analyses have shown a substantial reduction in mechanical complications, the number of attempts at required cannulation and the number of failed attempts at cannulation compared with the standard landmark placement when real-time 2-D ultrasound was used for placement (Hind et al. 2003; Randolph et al. 1996). Given these findings, it is likely that ultrasound guidance also reduces the risk of catheter-related thrombosis. Ultrasound guidance by an appropriately trained operator is now recommended for all nonemergent CVA procedures by several scientific bodies (Infusion Nurses Society 2006; Bishop et al. 2007; Calvert et al. 2004; Pratt et al. 2007).

2. Catheter flushing

Flushing of the catheter ports is routinely performed to maintain patency, reducing fibrin sheath and clot formation (Vescia et al. 2008). Since thrombosis is a major risk factor for CVC infection, catheter flushing is also performed to reduce the risk of catheter-related bloodstream infection (CRBSI). While the ideal flush solution, concentration, and the flushing interval have not been defined, protocols may be guided by individual manufacturer recommendations.

(a) Saline and unfractionated heparin are equally effective to prevent thrombotic complications. Heparin at doses of 500–5000 units has been the most commonly used agent. While long-term CVCs are usually flushed at least once a month, a recent retrospective study showed that CVCs flushed less frequently were not associated with an increased rate of catheter complications (Kuo et al. 2005). In patients receiving PN it is recommended that the catheter be flushed with saline when the infusion is complete or after a blood draw. Push-pause instillation (frequent stopping-starting of the flushing solution) should be used to create turbulent flow within the line. The minimum flush volume should be twice the catheter volume.
(b) Recombinant tissue plasminogen activator (rTPA) (1 mg in each lumen) applied weekly as a locking solution lowered the risk of catheter dysfunction and infection in hemodialysis patients (Hemmelgarn et al. 2011). A decrease in the number of catheter-related infections has been reported with the use of rTPA in patients with hemophilia (Ragni et al. 2008). Urokinase has similar efficacy as a locking solution for CVCs.

3. Low-dose systemic prophylactic anticoagulation/thrombolytics

Therapeutic warfarin has been associated with a 0.4–2% annual risk of nonintracranial hemorrhage and an annual intracranial hemorrhage risk of 0.1–0.9%, depending on the INR target range. There is inadequate evidence to support the routine use of low molecular weight heparin (LMWH), low dose vitamin K antagonists (warfarin 1–2 mg daily), vitamin K antagonists to maintain an INR between 1.5 and 2, continuous intravenous unfractionated heparin or fibrinolytics to prevent symptomatic catheter-related thrombosis in comparison to no prophylaxis (Ragni et al. 2008; Carrier et al. 2007; Kirkpatrick et al. 2007; van Rooden et al. 2008; Young et al. 2009).

Trouble-Shooting Catheter Occlusion

The patient should be referred to a physician if there is clinical evidence of DVT. If not, the first step toward restoring patency is to flush the catheter briskly with saline. If this is unsuccessful, the following steps should be undertaken to identify the cause:

1. Rule out mechanical problems
   (a) Examine the catheter for an over-tight retention suture that may be limiting flow.

(b) Attempt to aspirate blood with the patient in a supine, sitting, or standing position, with the ipsilateral arm raised.
(c) Radiograph to exclude an internal kink, fracture, or dislocation of the catheter.

2. Nonthrombotic occlusion

Lipid occlusion is treated with 70% ethanol or sodium hydroxide, mineral precipitates are treated with 0.1 N hydrochloric acid (HCl), drug precipitates are treated according to their pH, acidic drugs can be cleared with 0.1 N HCl, and basic medications can be cleared with sodium bicarbonate or 0.1 N sodium hydroxide (NaOH). A volume equal to the catheter fill volume should be instilled for up to 20 min.

3. Thrombotic occlusion
   (a) Thrombolytic Therapy

If mechanical and nonthrombotic occlusions have been ruled out, empiric administration of a thrombolytic agent should be performed. TPA is approved for restoring patency in CVA devices in the USA and Canada. One to two doses of Urokinase or rTPA may be administered and should be allowed to dwell for a period of 30 min to 2 h. In one study using rTPA (2 mg/2 ml), function was reported within 2 h in 90% of cases (Ponec et al. 2001). Similar results for rTPA were later confirmed in a large RCT including over 1,000 patients (Semba et al. 2002). Where thrombolysis is the indication for use, 1 mg rTPA is equivalent to 36,000 units of Urokinase. Protocols for incomplete and complete occlusions have been described and should be incorporated into the clinical practice guidelines at centers of expertise in IF. If patency is not restored, a physician should be consulted. Contrast study of the catheter should be performed if a thrombotic complication is suspected.

   (b) Endoluminal brushing is a procedure performed under aseptic technique in which a brush is attached to the catheter and then advanced through a sheath into the lumen until obstruction or the brush reaches its maximum position. After withdrawal, the catheter is aspirated, loose debris is removed and if patency is restored the catheter is then flushed with saline. The process can be repeated. The technique was successfully used to treat occlusions of long-term PN catheters at an IF center in the United Kingdom. It was then compared with their standard protocol for restoring catheter patency (urokinase +/− ethanol, HCL, or NaOH). Patency was restored in 86% of those treated with the endoluminal brush compared to 50% in those treated with the standard care (p < 0.0001). No complications were reported in either group (Allan et al. 2015).

   (c) Fibrin Sheath

Fibrin sheath formation is seen in up to 76% of short- or long-term CVC by pull-back venography (Oguzkurt et al. 2004). The sheath can form as early as 24 h after catheter insertion and encase its entire length within 5–7 days. Mechanical treatment options for dealing with a fibrin sheath include catheter exchange, disruption using a wire or angioplasty balloon, and fibrin sheath stripping. Such interventions are indicated when pharmacologic therapy fails to restore catheter tip patency. A retrospective review of 66 procedures performed in patients with poor flow through tunneled hemodialysis catheters despite rTPA administration showed similar cumulative catheter patency rates at 1 month, 3 months, and 6 months among the three groups: catheter exchange, fibrin sheath stripping, and fibrin sheath disruption. The results were similar to those reported elsewhere for fibrin sheath stripping and catheter exchange; cumulative patency rates of 31–93% at 1 month and 45–56% at 3 months (Janne d'Othee et al. 2006).

   (d) DVT
      (i) Anticoagulation

There is insufficient evidence to support the routine use of LMWH and a vitamin K antagonist or long-

term LMWH for the treatment of CVC-related thrombosis. Based on good evidence supporting the use of LMWH in lower limb DVT or pulmonary embolism in cancer patients, the International Society on Thrombosis and Hemostasis recommend the use of LMWH alone for a minimum of 3 months for the treatment of catheter-related thrombosis, depending on the clinical status of the patient (Debourdeau et al. 2013). To date, there have been no published data regarding the use of newer anticoagulants, such as fondaparinux, dabigatran, or rivaroxaban in the treatment of patients with upper extremity or catheter-related DVT.

(ii) Catheter removal

A catheter that is no longer required should be removed. If the catheter is functioning and CVA is needed then the device should be left in place and anticoagulation commenced. If the risk of pulmonary embolus is high, the catheter should be removed several days after commencing anticoagulation therapy, otherwise the catheter may be removed immediately. The patient should remain on anticoagulation for at least 3 months or as long as the CVC remains in place. Other indications for catheter removal include contraindication to anticoagulation or persistent symptoms despite therapeutic levels of anticoagulation.

(iii) Catheter or systemic thrombolysis

In patients with upper extremity-DVT, these therapeutic strategies have been studied only in small, retrospective case series (Sabeti et al. 2002; Vik et al. 2009). In the largest retrospective cohort study of systemic thrombolysis in upper extremity-DVT, the rates of DVT recurrence were similar between patients treated with thrombolysis or standard anticoagulation. However, systemic thrombolysis significantly increases the risk for major bleeding (15% vs. 0%) (Nayeemuddin et al. 2013). Catheter-directed thrombolysis may be safer, but data are limited (Vik et al. 2009). A thrombolytic or surgical approach is often considered in patients with extensive or massive thrombosis, but there is no evidence that such a strategy is superior over anticoagulant therapy alone in reducing the risk of recurrent thrombosis, pulmonary embolism, or post-thrombotic syndrome in patients with upper extremity-DVT (Kearon et al. 2008).

(iv) SVC filter placement

SVC filter placement should be limited to patients with a contraindication to anticoagulation therapy and to those with thrombus progression of symptomatic pulmonary embolism despite adequate treatment with anticoagulants. Placement of a SVC filter is technically more difficult than an inferior vena cava filter because of the shorter length of the SVC. In a review that included 209 patients treated with SVC filters, 3.8% had severe complications, including cardiac tamponade, aortic perforation, and recurrent pneumothorax (Owens et al. 2010). While mortality rates reported after filter placement are high, mortality is almost always related to the underlying disease (Mir 2008; Usoh et al. 2009).

Infectious Complications

The primary source of catheter-related infections in acute CVA devices is the patient's own skin (65%), the second most common source is the hub of the catheter (30%), and other pathways account

for 5% (Bouza et al. 2002). The hub is the primary source in long-term catheters. The most commonly identified organisms in catheter-related infections are coagulase-negative staphylococcus, *Staphylococcus aureus*, Candida species, enteric gram-negative bacilli, and *Pseudomonas aeruginosa* (O'Grady et al. 2002; Marschall et al. 2008). Multidisciplinary input from infectious disease, intensive care, and interventional radiology specialists is critically important for prevention and optimal management of catheter related infection. In 2011 the CDC and Healthcare Infection Control Practices Advisory Committee (HICPAC) published evidence-based guidelines for the prevention of intravascular catheter-related infections (O'Grady et al. 2011a). The incidence of catheter-related infection has been shown to be an important outcome quality indicator used to guide home PN care (Dreesen et al. 2013). Independent risk factors for catheter-related infection in patients receiving home infusion therapies included the administration of PN, multi-lumen catheters, and previous history of CRBSI (Raad et al. 1994).

A CRBSI is defined as at least two blood cultures positive with the same organism, obtained from at least two separate sites at different times, in association with evidence of colonization of the catheter with the same organism. An insertion site infection (ISI) is characterized by erythema, tenderness, and occasionally a discharge. A tunnel infection is characterized by pain and induration along the track of the catheter.

Preventive Measures

1. Education and training: Those responsible for the placement of CVA must ensure that healthcare personnel are educated and trained regarding the indications for intravascular catheter use, proper procedures for the insertion and maintenance of intravascular catheters, and appropriate infection control measures to prevent intravascular catheter-related infections. Knowledge of and adherence to guidelines by all personnel involved in the CVA service should be evaluated periodically (Dreesen et al. 2013). A randomized trial has provided evidence that interactive video-based education of both staff and patients reduces catheter-related infections in home PN patients and improves quality of life (Smith et al. 2003). There is some evidence that infection rates are reduced in home PN patients who are under the care of a dedicated nutrition support team (Dimick et al. 2003).
2. Hand hygiene by hospital personnel, caregivers, and the patients themselves is critical in the prevention of catheter-related infection. The CDI recommends washing with soap and water or waterless alcohol-based foams or gels.
3. Insertion technique and maintenance: The 2011 CDC Guidelines for the Prevention of Intravascular Catheter-Related Infections include step-by-step evidence-based recommendations relating to the prevention of catheter-related infection when inserting and maintaining these devices (O'Grady et al. 2011a). The catheter exit site and the hub should be cleaned regularly and every time the dressing becomes wet or contaminated. In a meta-analysis of eight randomized controlled trials in which chlorhexidine or povidone-iodine were used for site care of 4143 catheters in hospitalized patients, there was 49% less risk of infection when chlorhexidine was used (Chalyakunapruk et al. 2002). Chlorhexidine 2% is recommended for antisepsis of the hands, catheter exit site, and of the skin before catheter insertion (O'Grady et al. 2011a). Stopcocks, catheter hubs, and other sampling ports should always be disinfected, preferably using chlorhexidine 2% in 70% isopropyl alcohol. Intravenous administration sets should be changed every 24 h. Catheters that are no longer required should be promptly removed.
4. Site selection: While there remains some discussion regarding subclavian versus internal jugular placement of CVCs, there is general consensus that selection of an upper body insertion site should be considered to minimize the risk of infection in adult patients (Lorente et al. 2005; Merrer et al. 2001). A recent multicenter randomized trial involving 3027 ICU patients in whom nontunneled CVCs were

placed (Parienti et al. 2015) demonstrated lower rates of bloodstream infection and symptomatic thrombosis in subclavian vein catheterization compared to jugular-vein or femoral-vein catheterization. These findings must be weighed against certain increased risks associated with subclavian line insertion such as pneumothorax. Catheters should be placed as far as possible from open wounds, tracheostomies, stomas, or fistulae.

5. Device selection: The daily infection rate with CVCs is about 20 times higher than with peripheral catheters. The most serious CRBSI occur in the setting of short-term nontunneled catheters placed via central vein (Winkler 2005). The infection rate increases exponentially over time with their use. Rates of bacteremia are extremely high in nontunneled catheters within 2–4 weeks after placement (Nayeemuddin et al. 2013). In general, a lower rate of infection is documented with totally implantable devices (Leonidou and Gogos 2010). Long-term catheters that are tunneled (e.g., Hickman, Broviac, or Groshong catheters) appear to have one-quarter the daily risk associated with nontunneled central lines, but still pose a much higher risk than peripheral catheters. In one study, implanted ports had the lowest incidence of CRBSI (0.1 per 1,000 catheter days). In this same study the incidence of CRBSI among tunneled and nontunneled CVCs were 1.6 per 1,000 catheter days and 2.7 per 1,000 catheter days, respectively (Nayeemuddin et al. 2013).

   There is no consensus regarding infectious complications of PICC lines. Leonidou and Gogos (2010) found that PICCs seem to have a similar risk of infection to central lines in ICUs. In another study, PICC lines were associated with fewer CRBSIs in long-term surgical ICU patients (allowing for the fact that CVCs were in place somewhat longer than PICC lines) (Gunst et al. 2011). In this study, there were 263 CVCs and 37 PICCs placed. Of the CVCs, 4.9% became infected, an infection rate of 6.0 per 1,000 catheter-days. Of the 37 PICCs placed, 2.7% became infected, a rate of 2.2 infections per 1,000 catheter-days (Gunst et al. 2011).

   The use of catheters for hemodialysis is the most common factor contributing to bacteremia in dialysis patients (Jaar et al. 2000; Powe et al. 1999). The relative risk for bacteremia in patients with dialysis catheters is sevenfold the risk for patients with AVF (Hoen et al. 1998). If temporary access is needed for dialysis, a tunneled cuffed catheter is preferable to a noncuffed catheter, even in the ICU setting, if the catheter is expected to stay in place for >3 weeks (Vascular access work group).

   Polytetrafluoroethylene (Teflon®) or polyurethane catheters have been associated with fewer infectious complications than catheters made of polyvinyl chloride or polyethylene (Sheth et al. 1983). The use of anti-infective agents (aside from antibiotics) in conjunction with CVCs has been shown to reduce the rates of CRBSI for durations of between 5 and 12 days and greater than 20 days when CVCs are inserted in the femoral or jugular veins. Studies report the best clinical effect when CVCs are treated with a combination of minocycline and rifampin or internally and externally treated with silver or chlorhexidine and silver sulfadiazine (Brun-Buisson et al. 2004; Ostendorf et al. 2005; Rupp et al. 2005; Darouiche et al. 1999; Hanna et al. 2004b; Bong et al. 2003). Current evidence suggests that anti-infectives are cost-effective for high-risk patients compared with standard CVCs. Additional anti-infective agents demonstrated to have variable levels of efficacy include carbon and platinum, cuffs impregnated with silver, and benzalkonium chloride (Hockenhull et al. 2008).

   Catheter-related thrombosis is closely linked to CRBSI. Thrombus can serve as a nidus for infection. To this end, Wang et al. (2010) analyzed 45 trials with 12,085 enrolled CVCs. It was found that adjusted heparin-bonded catheters and minocycline/rifampicin catheters were associated with a significantly lower rate of CRBSI than standard catheters. It was concluded that rifampicin-based impregnated catheters were better for prevention of catheter-related infection compared with the

other catheters. Wang et al. also found that for prevention of CVC colonization, adjusted silver iontophoretic catheters, chlorhexidine and silver sulfadiazine catheters, chlorhexidine and silver sulfadiazine blue plus catheters, minocycline/rifampicin catheters, and miconazole/rifampicin catheters were associated with a significantly lower rate of catheter colonization compared with standard catheters (Wang et al. 2010). The ultimate conclusion of this large-scale meta-analysis was that rifampicin-based impregnated CVC was the only type of CVC that reduced both catheter colonization and CRBSI compared with standard CVCs and that rifampicin-based impregnated catheter seems to be more effective for prevention of catheter-related infection (Wang et al. 2010).

Other impregnated compounds have also been investigated. In critically ill patients, the use of silver-nanoparticle-impregnated CVCs had no significant effect on CVC colonization, CRBSI incidence or ICU mortality (Antonelli et al. 2012).

Infections are more common when CVCs with more lumens than are absolutely necessary are used.

6. Prophylactic antibiotics: Use of prophylactic antibiotics prior to CVA placement remains controversial and poorly studied. In one study that examined the use of prophylactic antibiotics in 404 patients prior to chest port placement, Karanalik et al. (Karanlik et al. 2011) found that Cefazolin 1 g given preprocedure had no significant impact on the already low rate of postoperative infectious complications (overall rate of surgical site infection was 2.7%). No difference in the incidence of infectious complications was found in either group. Covey et al. (2012) reached a similar conclusion in that the rate of early infection without antibiotic prophylaxis before chest port placement in the interventional radiology suite was only 1%. Based on their data, use of prophylactic antibiotics for implanted devices was not recommended. Additionally, there was no significant difference between the rates of device removal because of infections in patients who received antibiotics before the procedure versus patients who did not receive antibiotics. The CDC recommends against the routine administration of systemic antimicrobial prophylaxis before insertion or during use of an intravascular catheter to prevent catheter colonization or CRBSI (van de Wetering and van Woensel 2007). In nononcology patients, no benefit was associated with vancomycin administration prior to catheter insertion in 55 patients undergoing catheterization for PN (McKee et al. 1985). Extending perioperative prophylactic antibiotics in cardiovascular surgery patients did not reduce CVC colonization (Sandoe et al. 2003). For immunocompromised patients, administration of intravenous antibiotic prophylaxis should be considered on a case-by-case basis.
7. Topical applications: Several antibiotic and anti-infective agents have been tested at the surgical insertion site in an attempt to reduce catheter-related infection. In three RCTS involving hemodialysis patients, the use of 10% povidone iodine was associated with a significant decrease in colonization, exit-site infection, or bloodstream infection. The beneficial effect was most prominent in subjects with nasal colonization by *Staphylococcus aureus* (Fong 1993; Johnson et al. 2002; Levin et al. 1991). Mupirocin ointment applied at the catheter insertion site or nasally has been shown to reduce the risk of CRBSI; however, this has been offset by an increase in Mupirocin resistance in some centers and the potential for the drug to degrade polyurethane catheters.
8. Catheter locking: A solution is used to fill the catheter lumen and is left in situ while the catheter is not in use. Antibiotics, antiseptic agents (ethanol, taurolidine, and trisodium citrate) alone or in combination with anticoagulants (heparin, EDTA) have been used. There is insufficient evidence to support the prophylactic use of antibiotic lock solutions to prevent CRBSI. Furthermore, their use has generated concern relating to the development of microbial resistance. Heparin has not been shown to increase catheter-patency rates compared with saline and lacks antimicrobial properties at the

concentrations used in catheter lock preparations (Randolph et al. 1998; Goode et al. 1991; Peterson and Kirchoff 1991; Capdevila et al. 2001; Shanks et al. 2005). Seventy percent ethanol used as a catheter lock solution is associated with a reduced risk of CRBSI in a number of small studies of patients receiving home PN; however, increased risks of thrombosis and catheter structural changes have been reported (Metcalf et al. 2004; Maiefski et al. 2009; Opilla et al. 2007; John et al. 2012; Corrigan et al. 2013; Mermel and Alang 2014). Taurolidine a derivative of the amino acid taurine has broad ranging antimicrobial activity. Its use in a number of small studies has shown it to be safe; it does not increase microbial resistance and does not adversely affect catheter patency. A meta-analysis of six RCTs in which taurolidine or heparin were used as catheter lock solutions in 413 patients reported lower incidence of CRBSIs when compared to heparin locks (RR 0.34; 95% CI 0.21e0.55) (Liu et al. 2013). Catheter-related thrombosis was not increased with taurolidine use. At present, there are no recommendations for the routine use of lock solutions in CVCs.

Management

Diagnosis of CRBSI

Numerous studies and guidelines exist in the critical care and infectious disease literature regarding the methodology of diagnosing CRBSI. This is an important issue, as it was found in one study that more than 70% of the suspected CRBSIs yielded negative blood culture results (no growth), meaning that the catheter was unnecessarily removed (Deliberato et al. 2012). In that same study, there was no statistically significant difference between the standard and conservative methods of diagnosing CRBSI, with regards to in-hospital mortality. The standard method consisted of culturing the catheter tip, plus culture of a peripheral blood sample. The conservative method consisted of obtaining peripheral and catheter blood samples at different times with analysis of the number of colonies. Of the 29 deaths occurring in the ICU, 17 (58.6%) were from the conservative method group and 12 (41.3%) from the standard method group. The study showed no difference in mortality rates of patients with CRBSI when the two methods of diagnosis were compared. However, there was noted to be a difference in mortality when the standard method was compared to the conservative method in cases where the catheter is kept in place for more than 24 h (56% vs. 100%) (Deliberato et al. 2012). Nakazawa (2010) reported a much higher rate of false-positives with blood cultures obtained from catheters compared with peripheral sites due to catheter hub contamination.

In relation to the hematology/oncology patient population, certain aspects of diagnosing CRBSI are similar to those of the general population (Wolf et al. 2008). At least two of the following three symptoms are required to diagnose local infection: redness, induration, or tenderness within 2 cm of the venipuncture site. In patients with suspected or local infection without signs of systemic infection, two pairs of blood cultures should be taken, one from a peripheral vein and one from the CVC. The difference in time between positivity of results of catheter culture and peripheral blood culture has been found to be an important diagnostic indicator (differential time to positivity) (Wolf et al. 2008).

Catheter Removal or Retention

Convention has long dictated that after CRBSI has been demonstrated, the catheter is to be removed. However, in patients with limited access, this is often not feasible. In general, a catheter should be removed if the patient has unexplained sepsis or erythema overlying the catheter insertion site, purulence at the catheter insertion site, or if the CRBSI is associated with suppurative thrombophlebitis, endocarditis, or osteomyelitis (Leonidou and Gogos 2010). Catheters should also be removed in the setting of fungal CRBSIs. Of those with bacterial CRBSIs, 30–80% of catheters may be salvaged (Clare et al. 2008; O'Grady et al. 2011a). Catheter removal is advised if *Staphylococcus aureus* is isolated from blood cultures of a patient with an indwelling CVC. It has been

shown that attempts for catheter preservation in these subjects have no more than a 20% chance of success. Preservation of the catheter may be attempted in clinically stable patients, in whom coagulase-negative staphylococci, *Corynebacterium jeikeium*, *Acinetobacter baumannii*, *Stenotrophomonas maltophilia*, *Pseudomonas aeruginosa*, and bacillus species have been detected as infections. In clinically stable patients with fever of unknown origin, the catheter should not routinely be removed without microbiological evidence of catheter-related infection (Deliberato et al. 2012; Wolf et al. 2008). For infections localized to the exit site, treatment with antibiotics alone may be adequate. In uncomplicated infections where the catheter is to be retained, antibiotic lock therapy should be used for 2 weeks with systemic antibiotic therapy, based on culture sensitivities. In cases where the catheter is removed, a new long-term device should not be reinserted until a course of systemic antibiotic therapy has been completed and negative blood cultures have been obtained.

Leonidou and Gogos (2010) have stated that long-term CVC or ports should be removed from patients with CRBSI associated with any of the following conditions: severe sepsis, suppurative thrombophlebitis, endocarditis, bloodstream infection that continues despite 72 h of antimicrobial therapy to which the infecting microbes are susceptible, or if a port abscess is diagnosed. Salvage therapy can be considered in uncomplicated CRBSI where patients have limited access options and long-term intravascular access is required. Both systemic and antimicrobial lock therapy should be used, repeated blood cultures obtained, and the catheter removed if blood cultures remain positive for a microorganism when drawn 72 h after initiation of appropriate therapy (Leonidou and Gogos 2010).

Routine replacement of CVCs PICCs and hemodialysis catheters to prevent infection should be avoided in adults and children. Routine guidewire exchanges of nontunneled CVCs in an effort to prevent CRBSI should be avoided. In select patients with tunneled hemodialysis catheters and bacteremia, catheter exchange over a guidewire, in combination with antibiotic therapy, is an alternative as a salvage strategy in patients with limited venous access (Beathard 1999; Duszak et al. 1998; Robinson et al. 1998).

Treatment Recommendations

The microbes that colonize catheter hubs and the skin surrounding the insertion site are the source of most CRBSIs. The microorganisms involved in CRBSI have been shown, via electron microscopy, to be embedded in a biofilm matrix. Additionally, the number of organisms on the catheter tip is related to the occurrence of CRBSI (Leonidou and Gogos 2010). The microorganisms most often isolated from intravascular catheters are coagulase-negative staphylococci, followed by candida, *Staphylococcus aureus*, enterococcus, and pseudomonas, and acinetobacter (Leonidou and Gogos 2010; Yoshida et al. 2011). In a study of 296 patients receiving home PN, three quarters of CRBSIs were attributed to gram-positive organisms, 16% gram-negative organisms, 3% fungi, and 6% were polymicrobial infections (Santarpia et al. 2010)

(a) Coagulase negative staph: Coagulase negative staphylococci are the most common pathogens in CRBSIs. A diagnosis of bacteremia requires at least two positive blood cultures, including one drawn from a peripheral vein. While catheter removal may be sufficient to resolve the infection, it is generally recommended that the patient also be treated with 1 week of intravenous antibiotics. If the CVC is to be retained, a longer duration of therapy consisting of 10–14 days together with antibiotic lock therapy is advised. In the 20% of cases that fail to respond to these measures (persistent fever and/or bacteremia), the catheter should be removed (Raad 2000). Vancomycin, systemically and as a catheter lock therapy, is frequently used in institutions with a high prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA). Where MRSA isolates with vancomycin inhibitory concentration values >1 mg/mL are identified, alternative agents (e.g., daptomycin) should be considered (Mermel et al. 2009).

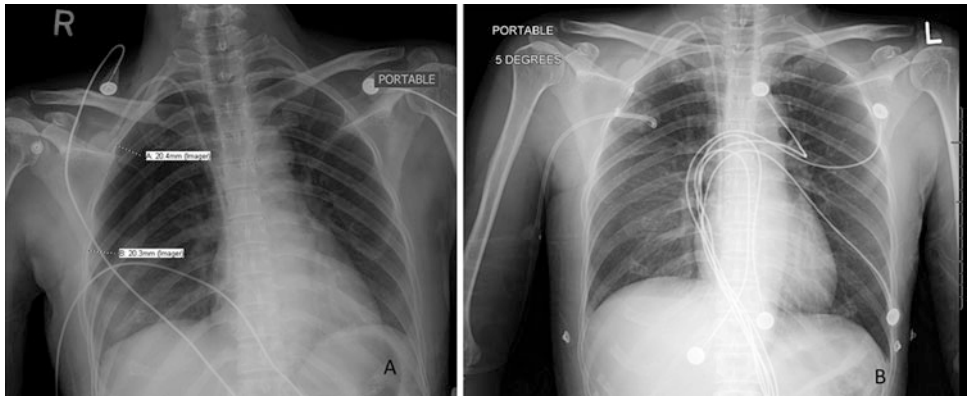

Fig. 1 (**a**) Chest radiograph AP projection demonstrates single lumen chest port placed via right internal jugular vein. The placement is complicated by a large pneumothorax. (**b**) Chest radiograph following placement of a right chest tube shows resolution of the pneumothorax

(b) *Staphylococcus aureus*: Catheter removal is advised if a nontunneled CVC is suspected to be the source of *Staphylococcus aureus* bacteremia, or in the case of a tunneled device, there is evidence of a tunnel infection or ISI (Semba et al. 2002). A new catheter should then be placed at a different site. Uncomplicated cases should be treated with intravenous antibiotics for a minimum of 10–14 days after catheter removal (Mermel et al. 2009). Caution should be exercised when considering catheter salvage. Failure or a delay in catheter removal has been associated with increased risk of hematogenous complications and increased mortality. The risk of such complications should be taken into account when deciding on the duration of therapy. Antibiotic treatment depends on sensitivities and may include penicillin, a first-generation cephalosporin, vancomycin, daptomycin, or linezolid (Leonidou and Gogos 2010).

(c) Enterococcus: The incidence of enterococcal infection associated with CVCs has increased substantially. The ability of the organisms to form a biofilm can make antimicrobial treatment more difficult. The Infectious Diseases Society of America (IDSA) guidelines for the treatment of enterocccal CRBSI caused by susceptible isolates advise either ampicillin or vancomycin alone or in combination with an aminoglycoside (Mermel et al. 2009). If ampicillin- and vancomycin-resistant enterococci are isolated, linezolid or daptomycin may be considered. If a long-term catheter is retained in cases of uncomplicated infection, 7–14 days of intravenous treatment is recommended in addition to antibiotic lock therapy (Fortun et al. 2006).

(d) Candida CRBSI: Candida species are the second commonest cause of infection in the setting of a vascular catheter and is associated with increased mortality, extended hospital stays, and high cost (Kojic and Darouiche 2004). Since catheter retention has been associated with poorer outcomes, catheter removal within 72 h is advised. The IDSA guidelines recommend antifungal therapy with fluconazole or an echinocandin for all CRBSI due to Candida species for 2 weeks after the last positive blood culture (Nayeemuddin et al. 2013). Data relating to antifungal lock therapies are lacking (Leonidou and Gogos 2010).

(e) Gram-negative bacilli: Data concerning the management of CRBSI due to gram-negative bacilli are limited. While the incidence of CRBSI due to gram-negative bacilli has decreased, multidrug resistance has become a concern. A high frequency of treatment failure and relapse has been documented if the CVC is retained (Hanna et al. 2004a). The

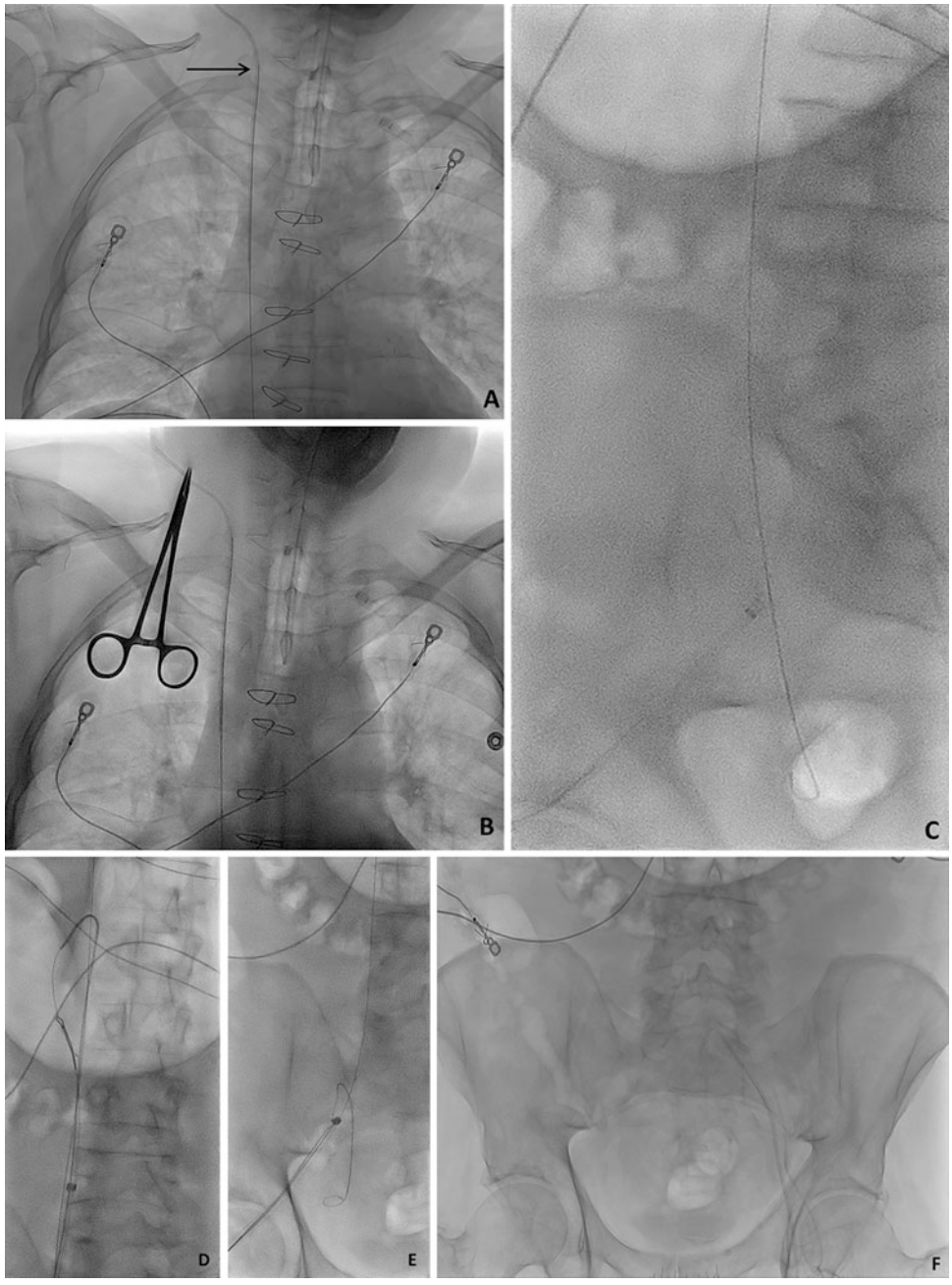

Fig. 2 (**a**) A CVC has been placed via right internal jugular vein. The guidewire is lost inside the catheter (arrow). (**b**) The hemostat denotes the skin entry site of the catheter. (**c**) LAO projection shows the tip of the J-wire in the right internal iliac vein and a sheath has been inserted via the right common femoral vein. Neither end of the J wire is accessible. (**d**) A reverse curve catheter is placed around the wire in the upper abdomen. A hydrophilic wire is advanced beyond the tip of the catheter and snared with a goose-neck snare device. The catheter is removed. The hydrophilic wire tip held by the snare is then pulled through the sheath.(**e**) Both ends of the hydrophilic wire are externalized and pulled until the guidewire is withdrawn into the right external iliac vein, into the sheath and removed. (**f**) The wire has been successfully retrieved. Left common femoral arterial and venous catheters are present

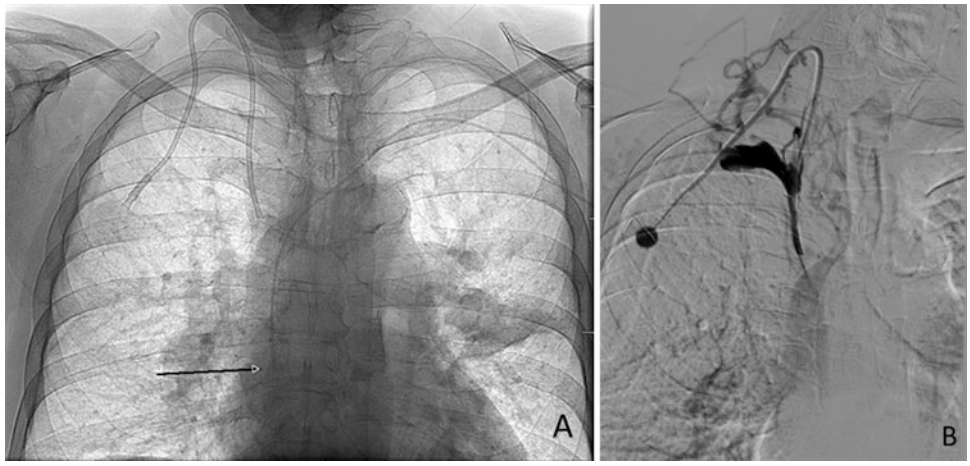

Fig. 3 (**a**) Single lumen chest port placed via the right internal jugular vein. The tip is malpositioned in the right brachiocephalic vein. The arrow indicates the correct position of a catheter tip at the cavoatrial junction. (**b**) Digital subtraction venography via the port reservoir demonstrates thrombosis and stenosis of the central right brachiocephalic vein. Multiple venous collaterals facilitate central venous drainage. The catheter was subsequently removed

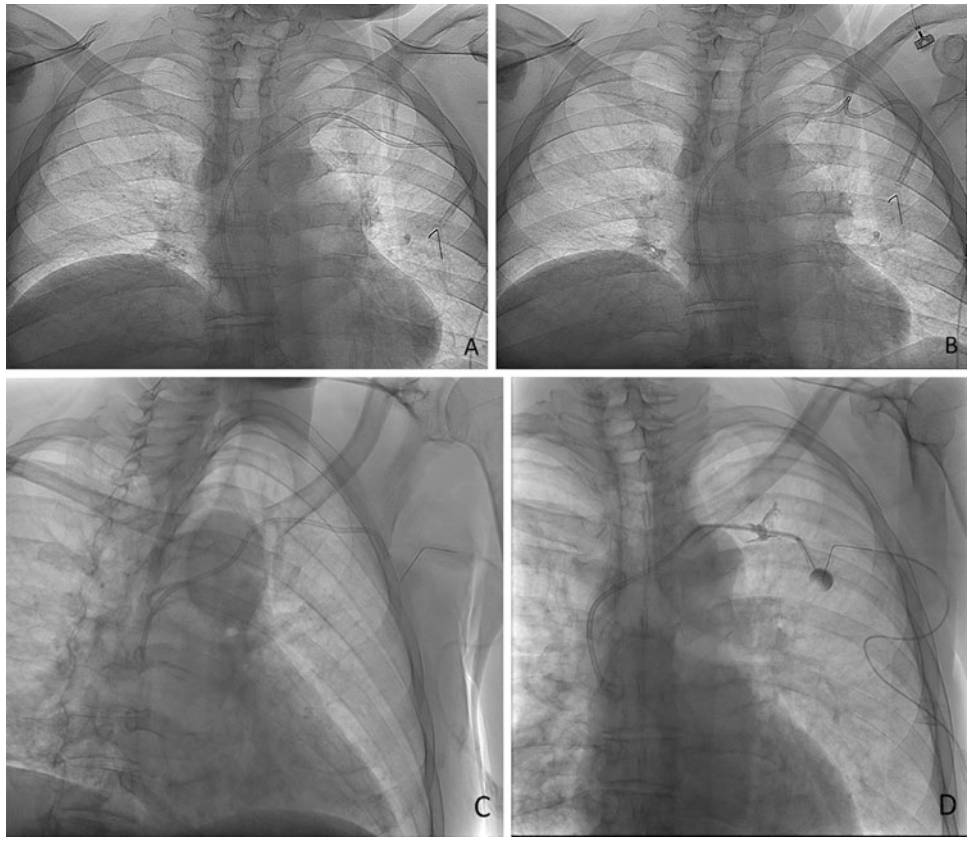

Fig. 4 (**a**) Single lumen chest port placed via the left subclavian vein. (**b**) Arm abduction demonstrates kinking and pinch-off of the catheter due to compression between the clavicle and the first rib. (**c**) Single lumen chest port placed via the left subclavian vein. No abnormality seen. (**d**) Catheter injection with contrast shows extravasation of contrast. The catheter is fractured due to pinch-off at the costoclavicular ligament

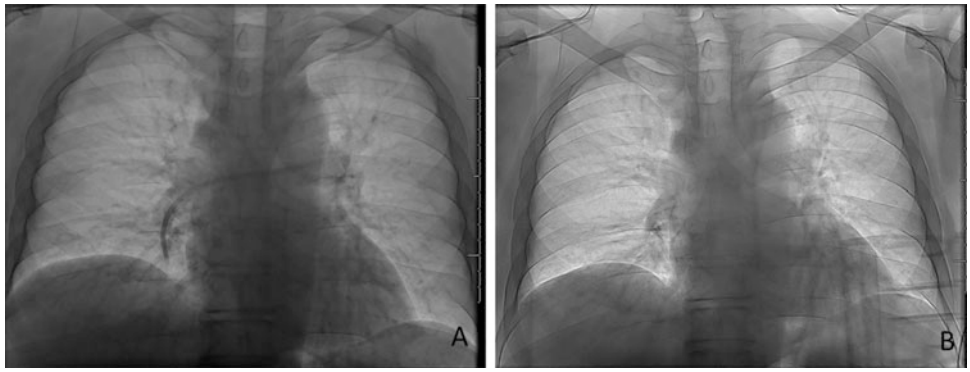

Fig. 5 (**a**) Single lumen chest port placed via the left subclavian vein. The catheter is fractured at the level of the costoclavicular ligament. The distal fragment has migrated into the right pulmonary artery. (**b**) The port was removed from the left chest wall and the distal fragment retrieved via right common femoral vein approach

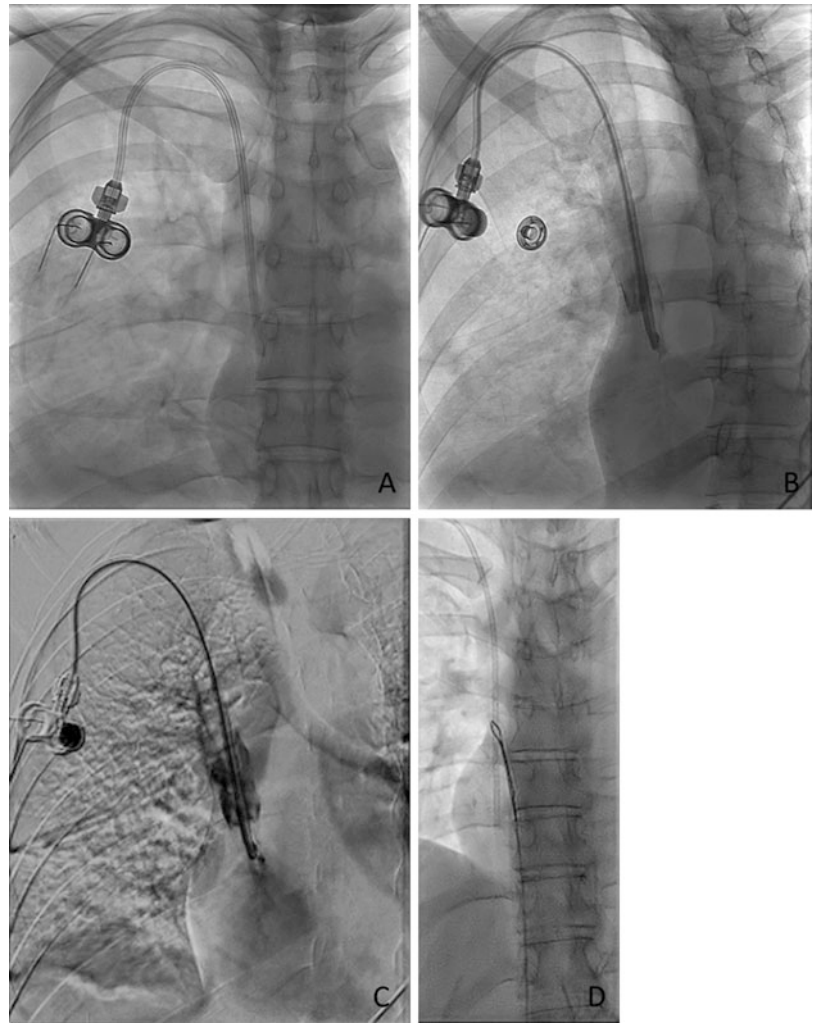

Fig. 6 (**a**) Single lumen chest port placed via the right internal jugular vein. (**b** and **c**) Digital subtraction venography via the port reservoir shows contrast refluxing superiorly between the catheter and the fibrin sheath. Filling defects in the mid-superior vena cava are consistent with peri-catheter thrombus. (**d**) Fibrin sheath stripping using an endovascular snare device

ISDA guidelines recommend empiric antibiotic therapy in septic, critically ill, or neutropenic patients, those with femoral catheter in place or those with known focus of infection as these patients are at higher risk for infection due to multidrug-resistant gram-negative bacilli (Mermel et al. 2009). Two different class of antimicrobial agents should be commenced in critically ill patients with suspected CRBSI and recent colonization of infection with a multidrug-resistant gram-negative bacillus until cultures and drug sensitivities become available.

Conclusion

CVA is required for intravenous supplementation in almost all forms of IF. The type and size of catheter placed will depend on the indication for and expected duration of treatment. Acute forms of IF are common in patients after abdominal surgery and can usually be successfully managed on the surgical floor. In the more complex unstable patient being managed in intensive care settings, the condition may be prolonged or progress to chronic forms. In recent years, the establishment of intestinal rehabilitation programs in IF centers of excellence have resulted in significant improvement in long-term survival of patients with chronic IF. The goals of care are to restore gut integrity, resume enteral feeding, and wean patients off PN. The multidisciplinary team should include an interventional radiologist and/or surgeon to guide the initiation and maintenance of CVA. Protocols to prevent and treat CVA complications should be evidence-based and monitored to ensure safety and efficacy.

Case 1 Pneumothorax
Patient reports dyspnea during chest port placement (Fig. 1).

Case 2 Guidewire-Related Complication
CVC placed at bedside following cardiac arrest. Guidewire lost (Fig. 2).

Case 3 Catheter-Related Thrombosis
Home PN nurse reports difficulty flushing the catheter and inability to aspirate blood despite administration of alteplase (Fig. 3).

Case 4 Pinch-Off Syndrome
Patient #1 reports intermittent difficulty aspirating blood and injecting fluids (Fig. 4a, b). Patient #2 referred for investigation of complete catheter occlusion (Fig. 4c, d).

Case 5 Catheter Fracture
Patient reports pain during injection of the catheter (Fig. 5).

Case 6 Fibrin Sheath
Home PN nurse reports inability to aspirate blood (Fig. 6).

Cross-References

- Modern Parenteral Nutrition
- Recent Evolution of Gut Rehabilitation
- Visceral Transplantation: Current Trends and Long-Term Outcome

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Recent Evolution of Gut Rehabilitation

Neha Parekh and Kareem Abu-Elmagd

Contents

Abstract

The past three decades have endorsed tremendous growth in the nutritional, medical, and surgical management of patients with complex abdominal pathology and gastrointestinal failure. As efforts to conservatively rehabilitate reached a plateau, innovative surgical techniques were developed to further enhance absorption, facilitate motility, and restore homeostasis to limited, diseased, or disordered bowel. Surgical strategies are highly individualized and are guided by the type of gut failure, residual gut anatomy, and surgical candidacy. Patient selection and evaluation is thoroughly discussed, and a new classification for surgical candidates with gut failure is introduced to guide the development of an optimal therapeutic plan.

Keywords

Surgical rehabilitation · Autologous gut reconstruction · Bowel lengthening and tapering · Bianchi · STEP · Surgical evaluation · Gut failure · Intestinal malrotation · Abdominal desmoids · Enterectomy · Motility disorder

Introduction

Since the clinical introduction of intestinal transplantation in the 1990s, the field of gut rehabilitation has witnessed significant advances in both medical and surgical management. Various innovative therapeutic modalities have been introduced to treat short bowel syndrome (SBS) and the

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complex abdominal pathology seen in disorders such as intestinal dysmotility, abdominal neoplasms, and splanchnic vascular thrombosis. These efforts continue to be fueled by the current limited indications and inherent potential complications of transplantation (Abu-Elmagd et al. 2015).

Novel approaches to gut rehabilitation developed over the last two decades have included tailored diet and medication regimens, new intravenous lipid emulsions, enterocyte growth factors, and surgical rehabilitation. Surgical intervention has traditionally been reserved for patients unable to attain enteral autonomy with medical efforts alone. However, recent reports have shown surgical therapy to be successful in reversing severe gastrointestinal (GI) dysfunction in subsets of patients failing diet and medical intervention, but not requiring parenteral nutrition (PN) (Abu-Elmagd et al. 2017a). In a series of over 300 patients collectively undergoing over 500 restorative procedures, primary causes of gut failure requiring surgical intervention included former technically flawed surgeries (32.5%), vascular disease (21%), gut dysmotility (14%), inflammatory disease (13%), congenital disorders (10.5%), and neoplastic disease (9%) (Abu-Elmagd et al. 2017a).

The therapeutic benefits of rehabilitative efforts are largely determined by the ability to control the primary disease, restore optimal gut function, improve transit time, prevent intraluminal bacterial overgrowth, and enhance overall gut absorptive capacity. When successful, surgical rehabilitation will improve existing GI function to achieve one or many of the following outcomes: (1) improved quality of life, (2) enteral autonomy, and (3) avoidance of need for intestinal transplantation. The ultimate goal of gastrointestinal rehabilitation in an SBS patient is to facilitate further adaptation and enable enteral autonomy, ensuring adequate growth and development of children or maintenance of normal weight and health in adults (Sudan and Rege 2014).

Surgical Techniques

Two of the most commonly used rehabilitative surgical techniques are autologous gut reconstruction and bowel lengthening and tapering. Autologous reconstruction with restoration of gut continuity has frequently been used for patients with complex enterocutaneous fistulae, recurrent strictures, or surgically bypassed bowel. These patients often have hostile abdomens with recalcitrant gut disorders following technically flawed former surgeries, possibly involving infected abdominal wall synthetic mesh. Many have chronic abdominal pain with refractory nausea, occasional vomiting, and generalized gut dysmotility. All complex surgical procedures should be performed using an open approach with placement of bilateral ureteric stents in patients with frozen abdomens to avoid incidental ureteric injury. Complete removal of any abdominal wall surgical mesh is necessary to avoid abdominal infection and prevent recurrent enterocutaneous fistulae and intra-abdominal abscesses (Abu-Elmagd et al. 2017b).

Each operation is an organ salvage procedure with conservative techniques guided by the area of the alimentary tract affected: foregut, midgut, and hindgut. Foregut reconstruction is commonly indicated for patients with a history of complicated esophagogastric surgery and for those with bariatric surgery-associated gut failure (Fig. 1, Abu-Elmagd 2015). This includes innovative surgical techniques used to create a neostomach with a visceral conduit such as a jejunal or colonic interposition in order to restore gut continuity in patients with a prior gastrectomy (Boukerrouche 2013, Fig. 2). Pyloroplasty is a beneficial adjunct to foregut reconstruction, especially in those with a retained antrum, to facilitate drainage of the denervated stomach (Abu-Elmagd et al. 2017b).

Midgut reconstruction involving one or more enteroenteric anastomoses to restore small bowel continuity is most frequently used in patients with mesenteric ischemia, Crohn's disease, and adhesive disorders (Fig. 3). Restoration of hindgut continuity via takedown of enterostomy, colostomy, or colonic fistulae is indicated even in patients with very little residual large bowel and a spared anorectum (Fig. 3). Residual colon and anorectum should be placed back into continuity to promote further gut adaptation and maximize absorptive surface area of the remaining bowel. Takedown

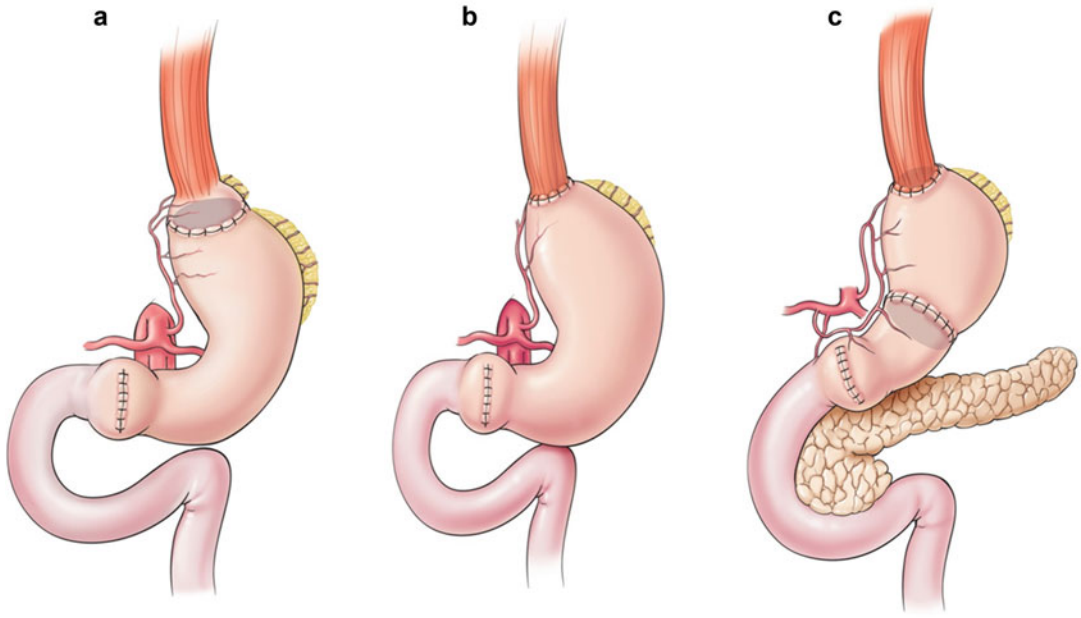

Fig. 1 Major foregut reconstruction with proximal gastrogastric (**a**), esophagogastric, (**b**) and combined esophagogastric and distal gastrogastric (**c**) anastomosis. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography. Copyright 2009–2018. All Rights Reserved)

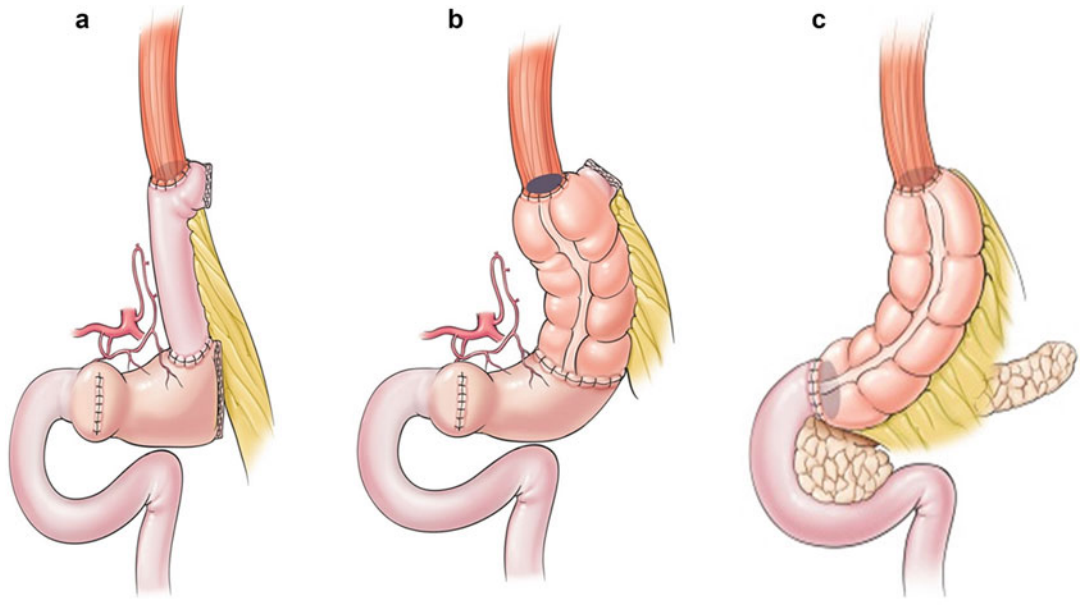

Fig. 2 A neostomach with an interposition visceral conduit to restore gut continuity in patients with prior complete or partial gastrectomy; jejunal interposition (**a**), colonic interposition with (**b**) and without (**c**) retained gastric antrum. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography. Copyright 2009–2018. All Rights Reserved)

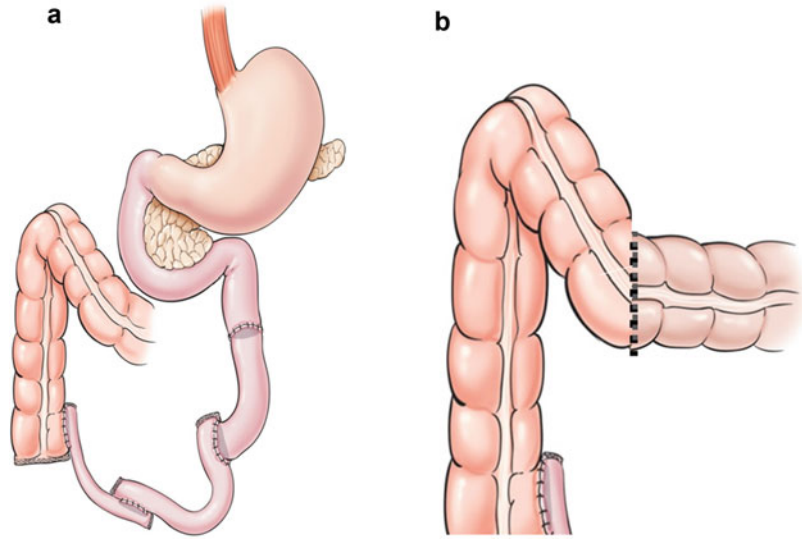

Fig. 3 Midgut reconstruction involving one or more enteroenteric anastomoses (**a**) and hindgut reconstruction via takedown of diversion (**b**) to restore gut continuity. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography. Copyright 2009–2018. All Rights Reserved)

of hindgut bowel diversion also allows for use of the alimentary tract to thereby stimulate biliary flow and minimize the cholestasis and steatosis commonly seen with ultrashort gut syndrome.

Bowel lengthening and tapering utilizing the Bianchi procedure or the serial transverse enteroplasty (STEP) is generally indicated in SBS patients with dilated, stagnant segments of small bowel suffering from refractory malabsorption and/or bacterial overgrowth. The Bianchi procedure longitudinally separates two leaves of the mesentery, each with their respective vascular supply, dividing the dilated bowel into two equal parts and anastomosing the two loops sequentially to double the length and half the diameter of the bowel (Fig. 4). The STEP procedure alternates mesenteric and antimesenteric stapler cuts, creating a zigzag-like channel that reduces diameter and increases length (Fig. 5).

Outcomes of both Bianchi and STEP are encouraging with enteral autonomy achieved in up to 60% of patients within the first few months of surgery when adjunct comprehensive medical management is applied, although long-term results suggest that only half of these patients are able to sustain benefit for up to 10 years (Sudan et al. 2007; Thompson et al. 2000). Repeat STEP is often necessary, particularly in patients who must resume PN, to increase transit time and enhance absorption in segments of re-dilated bowel. STEP is most often preferred over the Bianchi procedure as it is technically easier, minimizes risk of intraperitoneal contamination by avoiding need for reanastomosis, and reduces incidence of intestinal ischemia by preserving vascular anatomy of the bowel. Unlike Bianchi, STEP can be applied to dilated duodenal and colonic segments in addition to small bowel, and it can be performed after both Bianchi and prior STEP in cases of re-dilated bowel (Sudan and Rege 2014).

A less commonly used surgical therapy for SBS patients is the reversed intestinal segment, which was initially trialed in animals and more recently tested in both adults and children (Thompson 2004; Layec et al. 2013). The procedure has been proposed for patients with <80 cm remaining jejunum and no ileum or ileocecal valve, but with some remaining colon. It involves resecting a 10–15 cm distal jejunal segment, rotating it 180 degrees, and performing a reanastomosis between the remaining jejunum and proximal colon. Manometric recordings of small bowel activity in patients with reversed intestinal segments show that the surgery results in retrograde intestinal peristalsis to thereby delay intestinal transit and enhance intestinal absorption (Layec et al. 2013). However, patients undergoing the procedure are at risk for obstruction, and complete rotation of the mesentery may occur during the surgery, which may lead to intestinal ischemia (Sudan and Rege 2014).

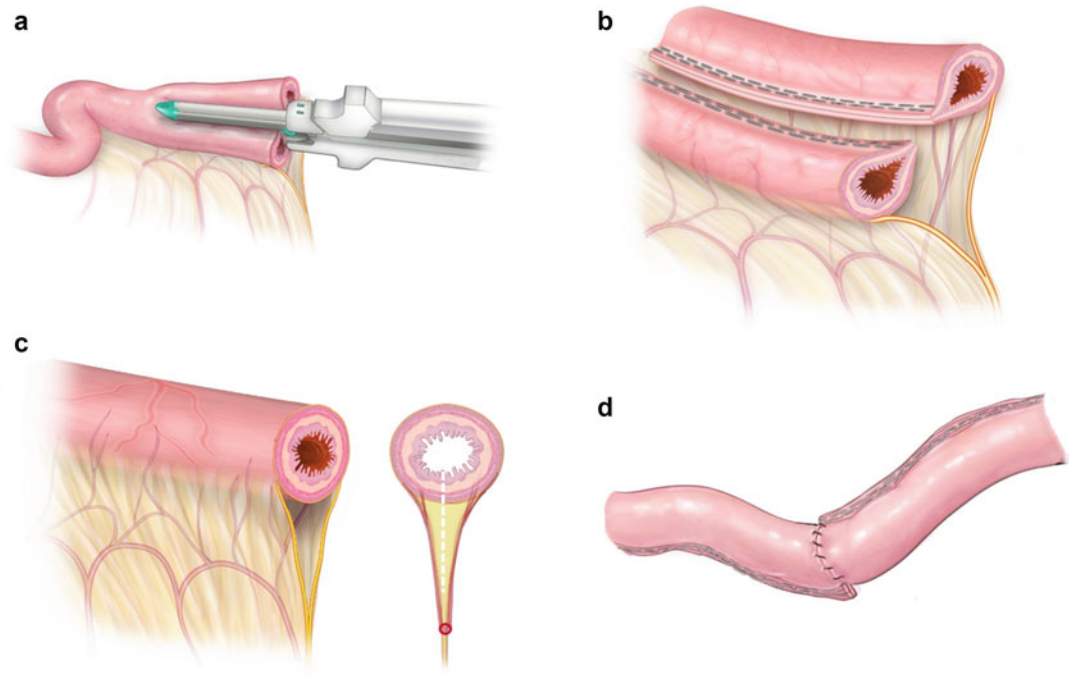

Fig. 4 Longitudinal (Bianchi) bowel lengthening. The Bianchi procedure longitudinally separates two leaves of the mesentery (**a**), each with their respective vascular supply (**b**), dividing the dilated bowel into two equal parts (**c**) and anastomosing the two loops sequentially (**d**) to double the length and half the diameter of the bowel. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography. Copyright 2009–2018. All Rights Reserved)

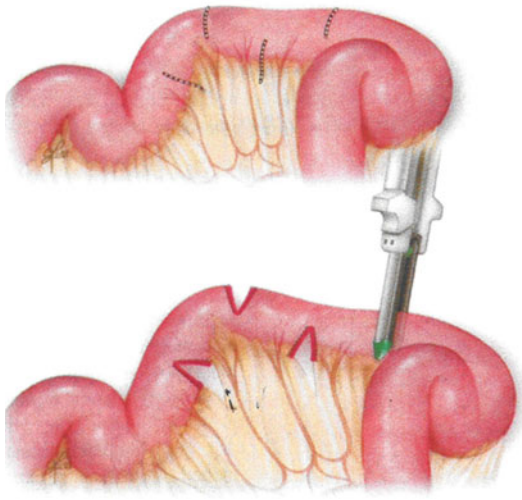

Fig. 5 Serial transverse enteroplasty (STEP). The STEP procedure alternates mesenteric and antimesenteric stapler cuts, creating a zigzag-like channel that reduces diameter and increases length. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography. Copyright 2009–2018. All Rights Reserved)

Patient Selection and Evaluation

Comprehensive preoperative planning is essential to design an optimal management plan, achieve a successful outcome, and minimize risk of postoperative complications. Patient selection requires a thorough investigation of past medical and surgical history, a complete awareness of any abnormal vascular or structural abnormalities, and an in-depth understanding of the underlying surgical disease and the residual gut anatomy (Table 1). Comorbidities such as smoking history, heart disease, diabetes, renal dysfunction, pulmonary disease, or vascular disorders may dictate additional testing and/or consultations to ensure viability of all organ systems before major abdominal surgery. Socioeconomic factors are also taken into consideration, especially for those traveling from long distances, to ensure both caregiver support and the financial means to sustain prolonged preoperative evaluation and postoperative recovery periods.

Table 1 Evaluation for surgical rehabilitation.

Component	Data
Past medical history	Comorbidities (i.e., smoking, alcohol, drugs, malignancy, immunodeficiency, hypercoagulability, disease of thoracic and/or abdominal organs)
Past surgical history	Operative and pathology reports Prior surgical consultations
Socioeconomic status	Availability of a dedicated caregiver Economic feasibility of a prolonged evaluation and/or recovery
Psychosocial factors	Severity of anxiety and depression Historical data on compliance
Gastrointestinal symptoms	Nausea, vomiting Abdominal pain, distention Diarrhea, constipation
Nutrition status	Weight history Anthropometrics Functional capacity
Anatomic and functional status of GI tract	Radiologic imaging Endoscopic instrumentation Histologic examination Motility testing
Cardiopulmonary status	EKG, echo, cardiac stress test CXR, CT chest, pulmonary function tests
Vascular system assessment	Hypercoagulable studies Visceral angiogram

The anatomic and functional assessment of the GI tract and of the other organs is key to the investigation process. Previous operative notes and pathology reports along with gastroenterology and surgical consultations are reviewed to piece together remaining anatomical configuration and trace progression of GI disease noting prior attempts at rehabilitation. Methods commonly utilized in evaluation of the GI tract include radiologic imaging, endoscopic instrumentation, histologic examination, and motility testing. Computerized tomography (CT) of the abdomen and pelvis with oral and IV contrast provides an outline of the remaining anatomy and mesenteric vascular supply and assists in viewing any dilation, narrowing, or stricturing of the intestine. Assessment of the level of dilation in the bowel is especially useful in deciding which SBS patients may benefit from the STEP procedure and in differentiating between patients with chronic intestinal pseudo-obstruction and those with generalized GI dysmotility.

Radiologic studies such as upper GI small bowel follow-through, enemas through the lower GI tract, and fistulograms are also useful in assessing remaining anatomy, bowel length, location of defects, and transit time along with any abnormalities. The timing of contrast studies is important as enteric contrast agents may produce artifacts on cross-sectional images; therefore CT scans should be done before enteric contrast studies (Lal et al. 2006). Water-soluble iodinated contrast agents are preferred to barium, especially when perforation or dehiscence is suspected, as there is a risk that extravasated barium may induce an inflammatory reaction in the peritoneum. Barium is not indicated for patients with motility disorders, as the contrast coats the intestines and can remain in the GI tract for prolonged periods of time to potentially worsen GI symptoms and interfere with other planned testing. Endoscopic instrumentation with histologic examination of the upper and lower GI tract is used to rule out active inflammatory bowel disease, growing polyps, GI varices, or malignancies. Patients with dysmotility syndromes often require gut motility studies including esophageal, antro-duodenal, and anorectal manometry, 4-h nuclear medicine gastric emptying studies, wireless motility capsule testing, defecography, and sitz marker testing to assess functional capability of each area of the GI tract.

The extent of assessment of the cardiopulmonary and vascular systems is guided by the patient age, the complexity of the past medical history, and the nature of the primary GI disorder (Abu-Elmagd 2008). All patients should have an electrocardiogram (EKG), whereas those above age 50 or with a history of coronary artery disease, hypertension, diabetes mellitus, smoking, or malignancy should also undergo cardiac stress testing with dobutamine. If the stress test is positive for ischemia, the patient will require a cardiac catheterization, and if the test is abnormal, cardiology should be consulted to provide surgical clearance. Similarly, all surgical candidates

should have a chest x-ray (CXR); however those at risk for aspiration pneumonia and/or granulomas such as SBS, desmoid tumor, or Crohn's disease patients and those with a smoking history should also undergo CT of the chest without contrast.

Vascular testing is required for all patients undergoing major abdominal surgery, and a non-invasive radiologic study such as CT abdomen with IV contrast is generally adequate to assess blood flow to the bowel. Those with radiologic evidence of partial or complete visceral venous thrombosis or patients with existing thrombotic disorders should undergo further testing to identify the underlying hypercoagulable state (Costa et al. 2010). The evaluation process includes measurement of protein C, protein S, antithrombin III, anticardiolipin, lupus anticoagulant, anti-phospholipid antibodies, and total homocysteine serum levels in addition to genetic studies for factor V Leiden, prothrombin G20210A, and JAK-2 gene mutations. When portomesenteric venous thrombosis is suspected or in cases of frequent systemic vascular thromboses, a visceral angiographic study including superior mesenteric and splenic arterial injections with venous phases is useful to evaluate the extent of thrombosis and to map the collateral circulation.

Specific Disease Considerations

As with nutrition and medical rehabilitation therapies, surgical strategies are highly individualized and are guided by the type of gut failure, residual gut anatomy, and surgical candidacy. A new classification describing the different types of gut failure (GF) has recently been introduced with respect to bariatric patients and may be extrapolated to all surgical candidates with gastrointestinal failure (Table 2, Abu-Elmagd 2015). Each type is defined by patient presentation, underlying etiology of GF, and associated pathophysiology.

Type-I GF includes those patients experiencing acute catastrophic gut loss due to internal herniation or vascular occlusion, most often left with ultrashort bowel syndrome. Early detection is crucial and patients with unexplained severe abdominal pain should be promptly explored despite nondiagnostic studies. Vascular shunts including the distal splenorenal shunt and the coronocaval shunt with gastric devascularization may be used in certain patients to restore portomesenteric circulation potentially as a bridge to transplantation (Costa et al. 2010). Those undergoing massive enterectomy leaving a short segment of the small intestine and full or partial colon may be candidates for gut reconstruction and/or STEP procedure in order to maximize remaining absorptive surface area. Restorative and lengthening procedures should be performed prior to implementing enterocyte growth factors such as GLP-2 (teduglutide) in qualifying patients unable to attain nutritional autonomy following surgery. Remaining absorptive surface area is maximized prior to trialing growth factor in order to allow for improved contact of nutrients with the enhanced intestinal mucosa.

Table 2 Surgical candidate classification based on type of gut failure

Type of gut failure (GF)	Cause
Type-I GF	Acute catastrophic gut loss due to internal herniation or vascular occlusion
Type-II GF	Technical complications following multiple corrective surgical interventions for recalcitrant disease
Type-III GF	Failure to thrive with progressive clinical dysfunctional syndromes

Type-II GF classifies those patients suffering major long-lasting technical complications, including GI fistulae, loss of gut continuity, and bowel obstruction after multiple corrective surgical interventions. Patients with recalcitrant disease such as Crohn's disease, radiation enteritis, and adhesive bowel disease may also fall into this category. These patients most often undergo gut reconstruction with restoration of GI continuity, particularly in patients with SBS. Various innovative techniques have been also developed to treat certain conditions such as intestinal malrotation, abdominal malignancy, and advanced mesenteric desmoid tumors.

Surgical complications are overall more common in the type-II GF population due to the nature of the diseased bowel and the elevated risk for

perforation, leakage, and intra-abdominal infection. A recent study of 118 patients undergoing elective ileostomy reversal showed that the need for immediate reoperation for surgical complications was strongly associated with a higher preoperative BMI ($p = 0.038$) and anemia ($p = 0.001$) (Schneider et al. 2016). These patients should be managed by a multidisciplinary team in a structured manner using the "sepsis-nutrition-anatomy-plan" algorithm which includes resolution of ***s***epsis, optimization of ***n***utritional status, definition of intestinal ***a***natomy, and delineation of a definitive medical and surgical ***p***lan (Calvert and Lal 2011).

Intestinal malrotation is a congenital anomaly involving rotation of the midgut with the duodenum failing to cross the midline, the majority of small bowel found on the right side of the abdomen, and the colon on the left. The dorsal mesenteric root of the small bowel is unusually narrowed leaving the midgut prone to volvulus and obstruction. Patients generally present with nonspecific abdominal pain and intermittent nausea and vomiting, making the diagnosis difficult without clear imaging on CT abdomen with oral contrast and/or upper GI small bowel follow-through. The Ladd procedure, introduced in 1936, remains the primary surgical technique used to correct intestinal malrotation through reduction of volvulus if present, complete lysis of coloduodenal (Ladd's) bands, widening of the base of the mesentery, re-positioning of the small and large bowel to proper quadrants, and prophylactic appendectomy (Frasier et al. 2015).

Over the past 3 years, the Cleveland Clinic Center for Gut Rehabilitation and Transplant has performed more than 45 innovative corrective operations for patients with intestinal malrotation, some having undergone Ladd procedures without sustained success. An open approach is used to take down all adhesions and rotate all abdominal organs back to proper anatomical position. Sutures are placed to anchor key areas to the abdominal wall including duodenopexy, cecopexy, mesenteriopexy, and left colopexy, and a prophylactic cholecystectomy and appendectomy are performed with partial colectomy in certain cases.

Creative efforts have also been made to treat abdominal malignancy not amenable to conventional resection in an attempt to avoid massive evisceration and intestinal or multivisceral transplantation (Tzakis et al. 2012). Ex vivo tumor resection with gut autotransplantation is a novel technique in which pathologic lesions are resected en bloc with midgut organs and the mesenteric vessels to provide tumor-free margins. The pathologic lesions are then resected ex vivo, the visceral vessels are prepared for reimplantation by either direct anastomosis or with interposition grafts, and the GI tract is reconstructed using conventional techniques. Of the ten patients reported to have undergone autotransplantation, seven had survived up to 12 years, six with functioning autografts and one after rescue with allotransplantation (Tzakis et al. 2012).

Advanced mesenteric desmoid tumors involving retroperitoneal organs are locally aggressive but histologically benign tumors traditionally considered unresectable and potentially fatal (Quintini et al. 2012). These patients are often burdened with severe abdominal pain leading to narcotic dependence, several abdominal drains to control GI losses and infection, and nephrostomies due to ureteric involvement. Piecemeal enterectomy with residual tumor debulking around the aorta, vena cava, ureters, and pelvic organs and ureteric reconstruction were performed in a series of seven patients followed by Osman et al. allowing all freedom from abdominal drains and nephrostomies and significantly reducing need for narcotics (Osman et al. 2017).

Patients with type-III GF are characterized by failure to thrive with progressive clinical dysfunctional syndromes, including motility disorders, restrictive intolerance in absence of mechanical pathology, and refractory gut malabsorption (Abu-Elmagd 2015). The clinical syndrome of restrictive intake includes an inability to eat, postprandial pain, anorexia, and other eating disorders often developing as a result of neurological deficits seen with severe malnutrition. Aggressive medical management with intensive psychiatric therapy is key to this population. Surgery should be reserved for those able to wean off narcotics and clearly demonstrate slow GI transit on motility testing.

Surgical intervention for the type-III GF population includes external venting, pyloroplasty, gastric pacing, gastrectomy, diverting ileostomy, abdominal colectomy with end ileostomy, and subtotal enterectomy with proximal enterostomy (Sogawa et al. in Press). Long-term success of these techniques is difficult to document due to the progressive nature of the disease.

Conclusion

A multidisciplinary team approach is crucial for the proper management of complex patients with varying degrees of gut failure. All patients with acute and chronic gut failure should be referred to specialty gut rehabilitation programs within tertiary care centers to potentially prevent transplantation and/or reverse gut failure. Successful restoration of nutritional autonomy of the native digestive system following surgical rehabilitation is dependent on the skill and experience of the multidisciplinary team. Failure to reestablish normal gut function and control adverse GI symptoms with potential weaning from PN should prompt early consideration for transplantation.

Cross-References

- ▶ Central Line Management and Intestinal Failure
- ▶ Current Management of Intestinal Failure in Children
- ▶ Modern Parenteral Nutrition

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Visceral Transplantation: Current Trends and Long-Term Outcome

Neha Parekh and Kareem Abu-Elmagd

Contents

Abstract

The successful development of visceral transplantation is one of the milestones in the recent history of human organ transplantation. All types of gastrointestinal transplantation have evolved to be the standard of care for patients with gut failure and complex abdominal pathology. The outcome has markedly improved over the last three decades due to technical innovation, novel immunosuppression, and better postoperative care. Recent data documented significant improvement in the long-term therapeutic indices of all types of visceral transplantation close to that achieved with thoracic and other solid abdominal organs.

Keywords

Intestinal transplantation · Parenteral nutrition · Visceral transplantation · Intestinal

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failure · Portomesenteric venous thrombosis · Transplant evaluation · Graft survival · Quality of life

Introduction

Prior to the introduction of parenteral nutrition (PN) in 1968, the condition of gastrointestinal (GI) failure was fatal. The use of PN significantly improved survival in patients with gut failure, although was soon linked with life-threatening complications such as catheter related sepsis, PN-induced liver disease, and line-associated thrombus. Unfortunately, the intestinal tract was considered a forbidden organ for clinical transplantation due to the associated massive lymphoid tissue, high antigenicity, and microbial colonization (Abu-Elmagd et al. 2009a; Grant et al. 2015). The practical application of visceral transplantation only became feasible after the 1989 advent of FK-506 (Prograf, tacrolimus) (Starzl 1989). New advances in surgical techniques, immunosuppressive strategies, and postoperative management allowed for the continual evolution of the procedure (Grant et al. 2005, Abu-Elmagd et al. 2009b).

In 2000, the US Centers for Medicare and Medicaid Services (CMS) qualified intestinal and multivisceral transplantation as the standard of care for patients with irreversible gut failure who no longer can be maintained on PN (Abu-Elmagd et al. 2002) Intestinal failure (IF) is defined as the inability to maintain nutrition or adequate fluid and electrolyte balance without intravenous (IV) support, due to severe impairment of the primary enteric digestive, absorptive, neuroendocrine, and/or motor functions (Abu-Elmagd et al. 2001). Irreversible IF is declared only after comprehensive medical and surgical rehabilitative measures that may control adverse symptoms, enhance gut function, augment adaptation, and/or treat the primary disease fail to allow weaning from PN. Resection of over 80% of the small bowel along with most of the colon and the ileocecal valve is usually associated with poor adaptation and the development of permanent IF.

Nomenclature

Visceral transplantation is a broad term encompassing isolated intestine, multivisceral, and any other combination of the visceral allograft with en bloc inclusion of the liver and/or pancreas (Fig. 1). In essence, the intestine is the central core

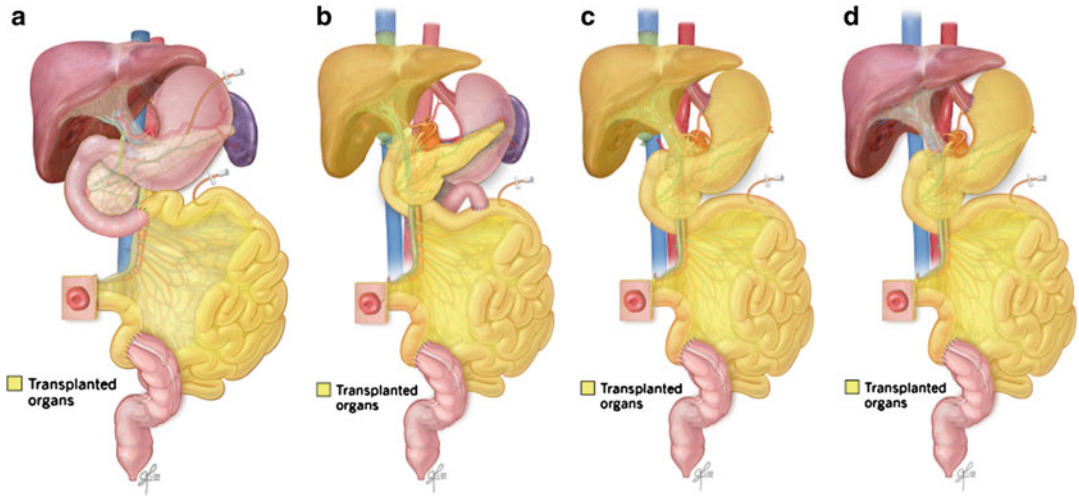

Fig. 1 The four main visceral allografts. (**a**) Isolated intestine. (**b**) Combined liver-intestine with en bloc pancreaticoduodenal complex. (**c**) Full multivisceral. (**d**) Modified multivisceral. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography. Copyright 2009–2018. All Rights Reserved; Buchman et al. 2003)

of any visceral allograft and the nomenclature is based upon the type and number of the organs that are transplanted en bloc with the intestine (Abu-Elmagd 2007; Fujiki et al. 2017). The term multivisceral is defined as en bloc implantation of the abdominal visceral organs including the stomach and intestine (Abu-Elmagd 2011). Multivisceral transplantation can be "full" or "modified" including the stomach, duodenum, pancreas, and intestine with and without the liver, respectively (Fig. 1c, d). The donor colon, spleen, and/or kidney can always be retained as secondary organs with any of these allograft types without the need for any further substratification (Fujiki et al. 2017).

Patient Selection

Despite major advances and continuously improved outcomes, intestinal transplantation is still mainly reserved for patients with irreversible IF who can no longer be maintained on PN (Abu-Elmagd 2015). According to worldwide data collected in the Intestinal Transplant Registry, the most common indication for visceral transplantation in adults remains SBS due to mesenteric ischemia (24%), recalcitrant Crohn's disease (11%), volvulus (8%), and trauma (7%) (Grant et al. 2015). Other frequent underlying pathology for visceral transplantation includes abdominal tumors (13%) such as Gardner's syndrome and motility disorders (11%) such as enteric dysmotility, primary hollow visceral myopathy or neuropathy, total intestinal aganglionosis, and secondary chronic intestinal pseudo-obstruction (Grant et al. 2015). Recently emerging indications for visceral transplantation are gut failure after bariatric surgery and diffuse portomesenteric venous thrombosis in patients with liver failure (Abu-Elmagd et al. 2017).

In conjunction with approving reimbursement for the procedure, CMS defined failure of PN and developed criteria for intestinal transplant, as outlined in the below list (Abu-Elmagd et al. 2002; Buchman et al. 2003).

List of Indications for Intestinal Transplant

Failure of PN (Abu-Elmagd et al. 2002)

1. PN-induced liver injury
   (a) Impending liver failure
      – Bilirubin above 3–6 mg/dL,
      – Progressive thrombocytopenia
      – Progressive splenomegaly
   (b) Overt liver failure
      – Portal hypertension
      – Hepatosplenomegaly
      – Hepatic fibrosis or cirrhosis
2. Central venous access device-related thrombosis of two or more central veins
3. Frequent central-line infection
   1. ≥2 episodes/year of systemic bacteremia requiring hospitalization
   2. Single episode of line-related fungemia
   3. Septic shock and/or acute respiratory distress syndrome
4. Frequent episodes of severe dehydration despite IV fluid in addition to PN

High Risk of Death Attributable to the Underlying Disease (Buchman et al. 2003)

1. Desmoid tumors associated with familial adenomatous polyposis
2. Congential mucosal disorders
3. Ultrashort bowel syndrome
   (a) Gastrostomy
   (b) Duodenostomy
   (c) Residual small bowel 10 cm in infants and 20 cm in adults

Intestinal Failure with High Mortality and Low Acceptance of PN (Buchman et al. 2003)

1. Intestinal failure with high morbidity or inability to function
   (a) Frequent hospitalization
   (b) Narcotic dependency
   (c) Pseudo-obstruction
   (d) High output stoma
2. Patient unwillingness to accept long-term PN (i.e., young patients)

Specific indications for intestinal transplant including IF-associated liver disease, recurrent catheter-related sepsis, and extensive vascular thrombosis limiting IV access have not changed over time (Grant et al. 2015). In addition to PN failure, nutritional failure is also considered a legitimate indication for transplantation. Nutritional failure is a new term that encompasses development of PN-related life-threatening conditions,

presence of ultra SBS, or diagnosis of end-stage GI disorders not amenable to medical and surgical rehabilitative measures (Hashimoto et al. 2015).

Early referral of patients meeting any of the conditions for visceral transplantation is critical, especially for those suffering PN-induced liver injury. Patients awaiting a combined liver-intestine transplant have higher mortality rate than those awaiting a liver transplant alone (Fryer et al. 2003). Early transplantation before development of nutritional failure or progression of complex abdominal pathology is commonly associated with positive outcome including preservation of the native liver and improved quality of life (Abu-Elmagd et al. 2012; Abu-Elmagd 2014). A 2009 report of 500 visceral transplants showed that PN use for <1 year pretransplant was a favorable predictor of improved survival after transplant (Abu-Elmagd et al. 2009b). Furthermore, the current survival after intestinal transplantation is comparable to that of patients with PN-dependent IF, despite the primary use of the procedure as a rescue therapy (Abu-Elmagd 2006).

Significant cardiopulmonary insufficiency, incurable malignancy, persistent life-threatening intra-abdominal or systemic infections, and severe immune deficiency syndromes with inability for prior successful stem cell transplantation are absolute contraindications to visceral transplantation (Abu-Elmagd et al. 2002, 2017). Lack of adequate social support is considered a relative contraindication due to poor long term survival and all efforts should be made to re-establish functional social support prior to transplant consideration (Abu-Elmagd et al. 2012). The presence of long-standing, controlled neuropsychiatric disorders should not preclude transplantation as successful rehabilitation postvisceral transplantation has recently been documented (Abu-Elmagd et al. 2012). Similarly, a history of GI malignancy, loss of central venous access, and older age are not absolute contraindications for transplant and should be considered on an individual basis within the context of the full evaluation.

Transplant Evaluation

Prompt referral of all IF patients to a center for gut rehabilitation and transplant may accomplish a two-fold objective: to explore opportunities for rehabilitation while capturing the critical window of opportunity for successful transplantation (Fishbein and Matsumoto 2006). Evaluation of the patient as a transplant candidate begins when all available medical and surgical options have been exhausted. The visceral transplant evaluation process is very similar to that of surgical rehabilitation (see ▶ "Recent Evolution of Gut Rehabilitation" chapter), with an added focus on establishing irreversible IF, determining organ requirements, and reviewing immunologic status. All transplant candidates are thoroughly educated and consented by the transplant nurse coordinator prior to undergoing comprehensive consultation with the multidisciplinary team. An in-depth biochemical analysis is also conducted on all candidates to assess nutritional, hepatic, renal, hematologic, and immunologic status as outlined in Table 1.

The anatomic and functional assessment of the GI tract and of the other organs is highly specialized, guided by the etiology of intestinal failure and clinical manifestations of extra-intestinal diseases.

Table 1 Visceral transplant evaluation

Component	Clinical data
Past medical history	• Smoking, alcohol, drug abuse • Heart disease, vascular disease, pulmonary disease, renal disease, diabetes • Liver disease, line infections, thrombosis of major central veins
Past surgical history	• Operative and pathology reports • Prior surgical consultations
Gastrointestinal symptoms	• Nausea, vomiting • Abdominal pain, distention • Diarrhea, constipation

(*continued*)

Table 1 (continued)

Component	Clinical data
Laboratory testing	• Nutrition panel • Hypercoagulable panel 1. Hematologic studies: protein C, protein S, antithrombin III, anticardiolipin antibodies, lupus anticoagulant, antiphospholipid antibodies and total homocysteine serum levels 2. Genetic testing: factor II, factor V Leiden, prothrombin G20210A, and JAK-2 gene mutations • Immune function panel/Hepatic serologies • Anti-HLA antibodies • Toxic drug screening • Tumor markers
Gut anatomy and functions	• Radiologic imaging • Endoscopic instrumentation • Histologic examination • Motility testing 1. Esophageal, antroduodenal, and anorectal manometry 2. Four-hour nuclear medicine gastric emptying studies: liquid and solid phase 3. Wireless motility capsule testing 4. Defecography and sitz marker testing
Status of native liver	• Radiologic imaging: CT abdomen, US liver 1. Hepatic steatosis, hepatomegaly, splenomegaly 2. Patency of hepatic vessels and biliary system 3. Degree of portal hypertension 4. Liver volumes • Endoscopic instrumentation 1. EGD: esophageal, gastric duodenal varices 2. Colonoscopy: rectal varices • Liver biopsy 1. Degree of cholestasis, steatosis, fibrosis, cirrhosis
Assessment of pancreatic function	• Insulin requirement • Amylase/lipase levels • Peptide-C level • HgA1C
Cardiopulmonary and vascular systems	• EKG, Echo, Cardiac stress test • CXR, CT chest, pulmonary function tests • Central vein mapping 1. Bilateral upper and lower duplex US 2. Bilateral upper and lower venograms • Mesenteric vascular supply 1.Visceral angiogram with superior mesenteric and splenic arterial injections with venous phases
Health Assessment	• Bone health 1. Bone densitometry: Osteopenia, osteoporosis 2. Parathyroid hormone (PTH), Vitamin D25 dihydroxy 3. Endocrinology consult • Breast, gynecologic and prostate health • Dental health
Multidisciplinary transplant team consultations	• Surgical • GI/nutrition • Psychosocial/socioeconomic • Infectious disease • Anesthesia

For patients with primary enterocyte disease such as radiation enteritis, autoimmune enteropathy, lymphangiectasia, and inflammatory bowel disease, a full radiologic, endoscopic, and pathologic examination of the residual GI tract is essential. Patients with dysmotility and pseudo-obstruction syndrome should undergo GI motility studies to define the type and extent of their disease. Candidates with thrombotic disorders require hematologic studies to identify the underlying hypercoagulable state and abdominal visceral angiography to assess patency of the splanchnic vascular system. In these and other high-risk candidates such as long-term PN-dependent patients, imaging of the upper and lower central veins is essential to establish adequate venous access at the time of surgery. Desmoid tumors should be assessed with a CT angiogram of the abdomen and/or chest to define the extent of the lesion(s) and its relationship to the adjacent vital structures.

An accurate assessment of the extent of PN-associated liver injury is very crucial for successful outcome after transplantation. PN-induced liver disease is frequently under diagnosed and may be present long before elevations in serum transaminases and bilirubin (Chan et al. 1999; Fishbein 2009). The diagnosis of portal hypertension is based upon standard criteria including low blood cell counts, a low platelet count, an enlarged spleen, the detection of gastroesophageal varices or portal hypertensive gastropathy, and the presence of ascites (Abu-Elmagd 2008). Some of these overt manifestations are less pronounced in patients with SBS due to reduced or absent mesenteric arterial flow. All transplant candidates on long-term PN independent of biochemical evidence of liver injury should undergo liver biopsy either at the time of prior attempt for surgical rehabilitation or during the transplant evaluation. A transjugular liver biopsy with bilateral upper and lower venograms may be performed simultaneously in interventional radiology to assess patency of the central venous system. In addition, a computed tomography (CT) of the abdomen with IV contrast is needed to provide imaging of the hepatic vessels, assess degree of portal hypertension, and determine coexistence of any other abdominal organ diseases.

Types of Visceral Transplantation

There are fundamentally four types of gut transplantation: isolated small bowel transplant, liver-small bowel transplant with pancreas en bloc, multivisceral transplant, and modified multivisceral transplant (Table 2). Transplantation with different combinations of en bloc abdominal visceral organ replacement has been used successfully in patients with various end-stage GI disorders (Abu-Elmagd et al. 2002). Patients with chronic IF are candidates for intestinal transplant either alone, combined with liver and/or pancreas, or as part of a multivisceral graft. The type of transplant required depends on the underlying etiology of IF, quality of the native organs, presence/severity of liver disease, and history of prior abdominal surgeries. In all cases, a vent chimney or simple loop ileostomy is performed to monitor graft rejection and provide easy access for frequent surveillance endoscopy with random mucosal biopsies. Surgical closure of these vents is performed 12–24 weeks after transplantation guided by the postoperative course and functional recovery of the intestinal graft. Gastrostomy and jejunostomy tubes may also be inserted immediately following transplant for postoperative decompression and early enteral feeding.

The general indications for all types of visceral transplantation are outlined in Table 2. When native hepatic functions are preserved, most patients with irreversible IF undergo isolated intestinal transplantation (Fig. 1a). In patients with concomitant failure of other organs, such as those with insulin-dependent diabetes (beta cell failure) and/or end stage renal disease, the pancreas and/or kidney is procured en bloc and simultaneously transplanted with the intestinal allograft. The decision to perform simultaneous hepatic replacement is very challenging, particularly in patients with asymptomatic portomesenteric venous thrombosis and significant liver damage. In general, patients with modest portal hypertension including mild splenic enlargement, platelet count >50,000, no gastroesophageal varices, and portal fibrosis without significant hepatic

Table 2 Types of allografts

Transplant procedure	Organs included	Indications
Isolated intestinal	Intestine +/− colon, kidney, pancreas	Intestinal failure *without* severe PN-induced liver disease
Combined liver and intestine	Liver, pancreatico-duodenal complex[a], intestine +/− colon, kidney	Intestinal failure *with* severe PN-induced liver disease
Full multivisceral[b]	Stomach, duodenum, pancreas, intestine, liver +/− colon, kidney	Diffuse gut disorders such as dysmotility syndromes, intraabdominal tumors that require extensive evisceration, massive gastrointestinal polyposis, traumatic loss of the abdominal viscera, or portomesenteric venous thrombosis with hepatic decompensation
Modified multivisceral[b]	Stomach, duodenum, pancreas, intestine +/− colon, kidney	Preserved hepatic functions in patients with diffuse gut disorders

[a]Pancreas and duodenum are included in the liver-intestine transplant block for surgical technical reasons, as they share the same axial blood supply with liver and intestine
[b]With possible preserved native pancreaticoduodenal complex and/or spleen

cholestasis should be cautiously considered for intestinal transplantation alone.

A composite liver-intestinal allograft with en bloc pancreaticoduodenal complex is reserved for patients with irreversible liver damage and irreversible IF (Fig. 1b). The procedure should also be considered for patients with liver failure and concomitant thrombosis of the portomesenteric venous system. Criteria for a combined liver-intestine transplant include documented end-stage hepatic disease associated with refractory ascites, spontaneous bacterial peritonitis, refractory variceal bleeding, chronic encephalopathy, hepatorenal syndrome, failure to thrive, and a severe compromise in quality of life (Abu-Elmagd et al. 2001). Additionally, posttransplant survival rates are higher for combined liver-intestine recipients compared with isolated intestine recipients due to proven immunologic benefits of the liver (Abu-Elmagd et al. 2009b).

Full or modified multivisceral transplantation is the only available treatment for patients with irreversible failure of their abdominal visceral organs including the small bowel (Fig. 1c, d) (Hashimoto et al. 2015). It is indicated for symptomatic extensive thrombosis of the splanchnic vascular system, massive GI polyposis or other premalignant neoplasms, and generalized GI dysmotility syndromes. In patients with gut dysmotility and in select patients with extensive abdominal desmoid tumors, the native pancreaticoduodenal complex, including the spleen, may be preserved during a full or modified multivisceral transplant (Fig. 2). Benefits of this include a reduced risk of post-transplant lymphoproliferative disorder (PTLD), elimination of need for biliary reconstruction, and augmentation of islet cell mass with retention of native pancreas (Sogawa et al. 2017; Cruz et al. 2010, 2011).

Inclusion of the donor colon is an option for patients with prior total proctocolectomy and preserved internal and external anal sphincters deemed suitable candidates for a pull-through operation (Fig. 3) (Abu-Elmagd et al. 2017). In a review on colon inclusion in the intestinal graft, improvement was noted in quality-of-life indicators, stool patterns, fecal continence, and parenteral nutrition weaning in recipients of colonic inclusion (Matsumoto et al. 2011). The authors concluded that colon inclusion has no adverse effects and may provide necessary physiologic functions of water absorption, residue breakdown, and storage. The Intestinal Transplant Registry (ITR) has also reported that inclusion of the colon had no adverse effect on survival and those with a donor segment of colon had a 5% higher rate of independence from supplemental PN than visceral transplant recipients without donor colon (Grant et al. 2015).

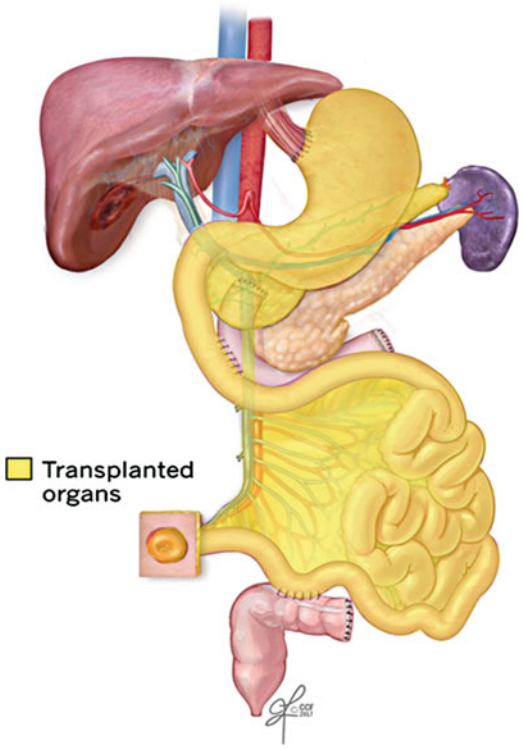

Fig. 2 Modified multivisceral transplantation with preservation of the native spleen and pancreas. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography. Copyright 2009–2018. All Rights Reserved; Buchman et al. 2003)

Recipient Surgical Technique

In addition to modification of the donor procedure with inclusion of different donor visceral organs, innovation of the recipient operation has been one of the landmarks of the recent evolution of visceral transplantation. Modifications to both the vascular and gastrointestinal reconstruction operations have been largely driven by organ shortage in the milieu of patients with complex abdominal pathology.

Vascular Reconstruction

The arterial inflow of the isolated intestinal graft is restored by anastomosing a free donor arterial segment, mostly iliac or carotid, to the recipient infrarenal abdominal aorta or iliac arteries particularly in patients who are undergoing retransplantation with an isolated intestinal graft (Fig. 4). The technique of anastomosing a vascular conduit to the recipient vessels rather than to the allograft mesenteric vessels on the back table avoids difficult exposure and possible prolongation of the warm ischemia time (Abu-Elmagd et al. 2000). In addition, the initial in situ placement of a free donor arterial and venous conduit facilitates a safe vascular reconstruction before bringing the visceral allograft to the operative field (Abu-Elmagd et al. 2000). The venous drainage depends primarily on the technical feasibility of gaining access to the recipient portomesenteric axis. Portal venous drainage (Fig. 4) should always be attempted in patients with inadequate hepatopetal portal flow, previous splenectomy, de-arterialized native liver, and those with caval filters. The systemic caval drainage is used in patients with frozen hepatic hilus, portal vein thrombosis, significant hepatic fibrosis, and prior intestinal transplant (Fig. 4).

The different types of vascular reconstruction of the composite visceral allograft are depicted in Fig. 5a. Nonetheless, the most commonly used arterial vascular reconstruction is the Carrel patch technique utilizing an arterial conduit that is anastomosed to the common aortic patch that contained the orifices of the celiac trunk and superior mesenteric artery (Fig. 5b). For the combined intestinal and pancreas transplantation, a bifurcated aortic graft is commonly utilized on the back table and anastomosed to the superior mesenteric and splenic arteries of the allograft (Fig. 5c). The venous reconstruction of the liver contained visceral allograft is through the common confluence of the native hepatic veins utilizing the piggyback technique (Fig. 6). In recipients with retained native left upper quadrant organs, a portocaval shunt is performed between the retained short segment of the native portal vein and inferior vena cava (Fig. 6). It is important to emphasize that the standard retrohepatic caval replacement is rarely needed and the previously adopted porto-portal shunt is no longer practiced at our center (Fig. 6). With the liver-free composite visceral graft, the venous drainage is commonly portal and similar to the isolated intestinal

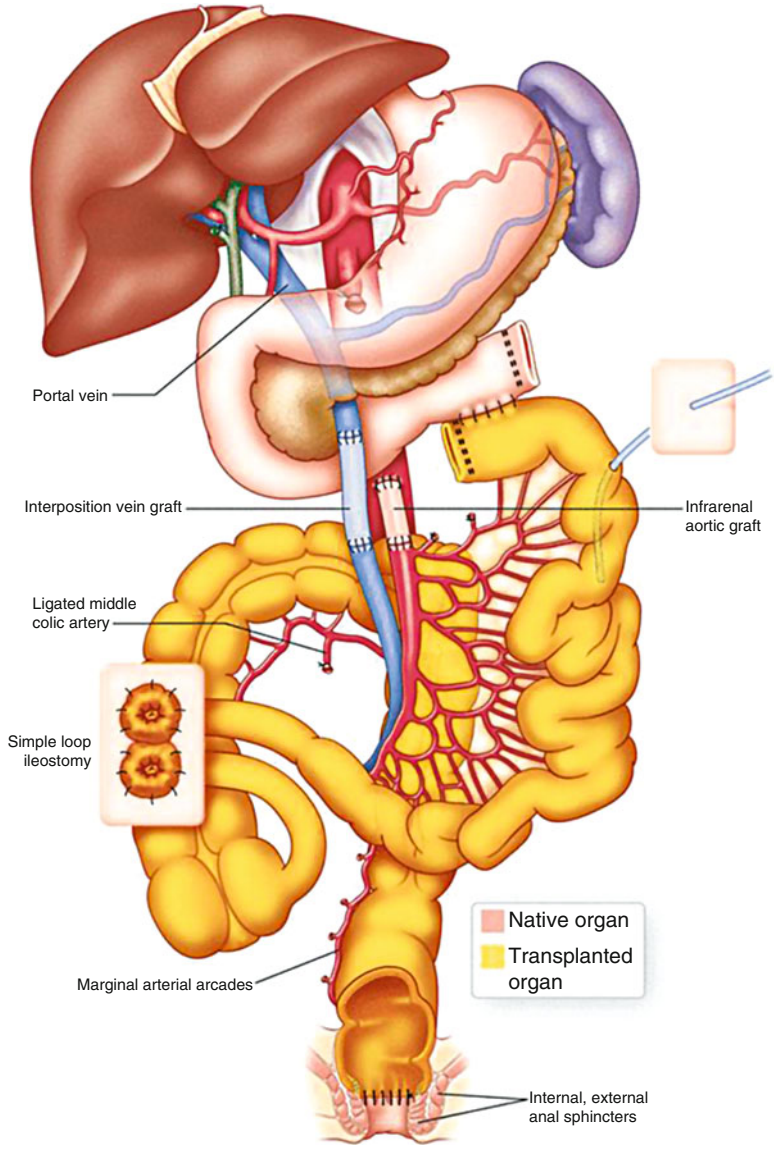

Fig. 3 Pull through reconstruction with en bloc colon and intestinal transplantation in a patient with intact anal sphincters. (Nyabanga C, Kochhar G, Costa G, et al. Management of Crohn's disease in the new era of gut rehabilitation and intestinal transplantation. Inflamm Bowel Dis 2016; 0:1-14, by permission of Crohn's & Colitis Foundation of America, Inc.)

allograft utilizing the short segment of the donor portal vein to drain the contained organs including the stomach, duodenum, pancreas, and the intestine.

Gut Reconstruction

Restoration of gastrointestinal continuity is generally achieved using conventional surgical techniques. With isolated intestinal and combined liver-intestine transplantation, the proximal anastomosis is performed between the native duodenum or jejunum and the allograft jejunum with different anastomotic techniques (Fig. 7a–c). In selected cases with ultra-short duodenum, a native colonic conduit is utilized for reconstruction to avoid the need for a more composite allograft (Fig. 7d). With full or modified multivisceral transplantation, foregut reconstruction involves anastomosing the transplanted stomach to the native esophagus or the residual gastric cuff (Fig. 1c, d). In addition, a pyloromyotomy or pyloroplasty is required to drain the denervated allograft stomach.

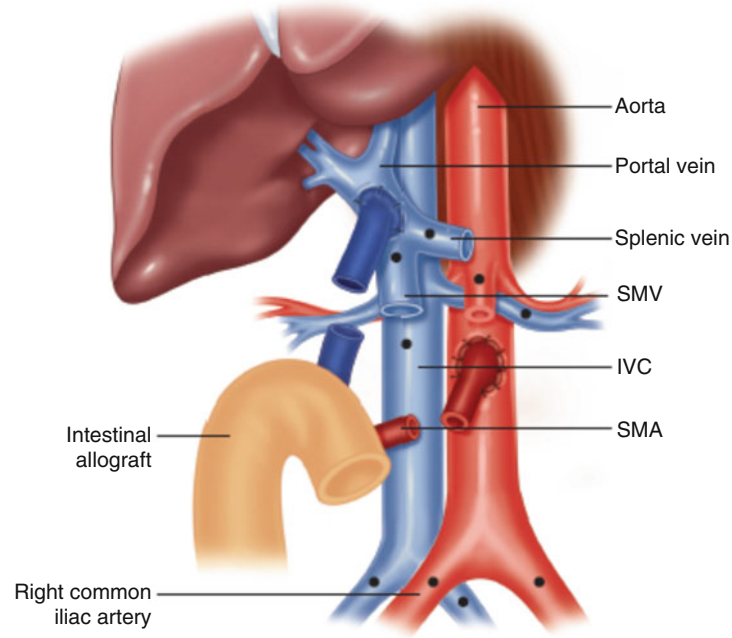

Fig. 4 Arterial and venous vascular reconstruction of the intestinal allograft. Early in situ vascular grafting is performed by anastomosing a free donor arterial and venous vascular graft in the recipient before bringing the intestinal allograft to the operative field. The infrarenal aorta or common iliac artery (CIA) is used for the arterial inflow. The portal vein (PV), superior mesenteric vein (SMV) or splenic vein (SV) is used for portal venous drainage and the inferior vena cava (IVC) for systemic drainage. The multiple options are labeled with *black dots*

A piggyback duoduodenal anastomosis is also required for patients with preserved native duodeno-pancreatic complex (Fig. 2). Distal gut reconstruction is restored in patients with residual hindgut by anastomosing the allograft ileum to the native colon or rectum. For endoscopic allograft monitoring, a diverting chimney (Fig. 8a) or simple loop ileostomy (Fig. 8b) is created and an end ileostomy is done in patients with prior proctocolectomy (Fig. 8c).

Postoperative Management

Immunosuppressive therapy, early diagnosis of allograft rejection, infectious prophylaxis, and nutritional management are the primary components of posttransplant care. The introduction of novel immunosuppressive agents and the refinement of immune modulatory strategies have improved the therapeutic efficacy of visceral transplantation. The use of recipient preconditioning with lymphoid-depleting agents combined with posttransplant minimal immunosuppression has led to improved survival with reduced incidence of intractable rejection, PTLD, and fatal infections.

With no currently available biochemical or biological markers of rejection, surveillance endoscopy with multiple mucosal biopsies is the only tool to diagnose intestinal rejection. Endoscopic findings of mucosal erythema or ulceration and histologic evidence of allograft injury including crypt damage, apoptosis, and sloughing of the intestinal mucosa may be seen with acute rejection. Clinical signs of acute rejection may include fever, diarrhea or high stoma output, abdominal distention, leukocytosis, thrombocytopenia, or GI bleeding. With chronic rejection, recipients may present with weight loss, severe malnutrition, GI bleeding, bowel obstruction, and enterocutaneous fistulae with full-thickness histopathologic evidence of cryptopenia, obliterative arteriopathy, mesenteric sclerosis, and lymph node depletion. Increasing dosing of immunosuppression with steroids and antilymphoid preparations is required for treatment of acute rejection, and advanced chronic rejection may be treated with allograft enterectomy and/or retransplantation.

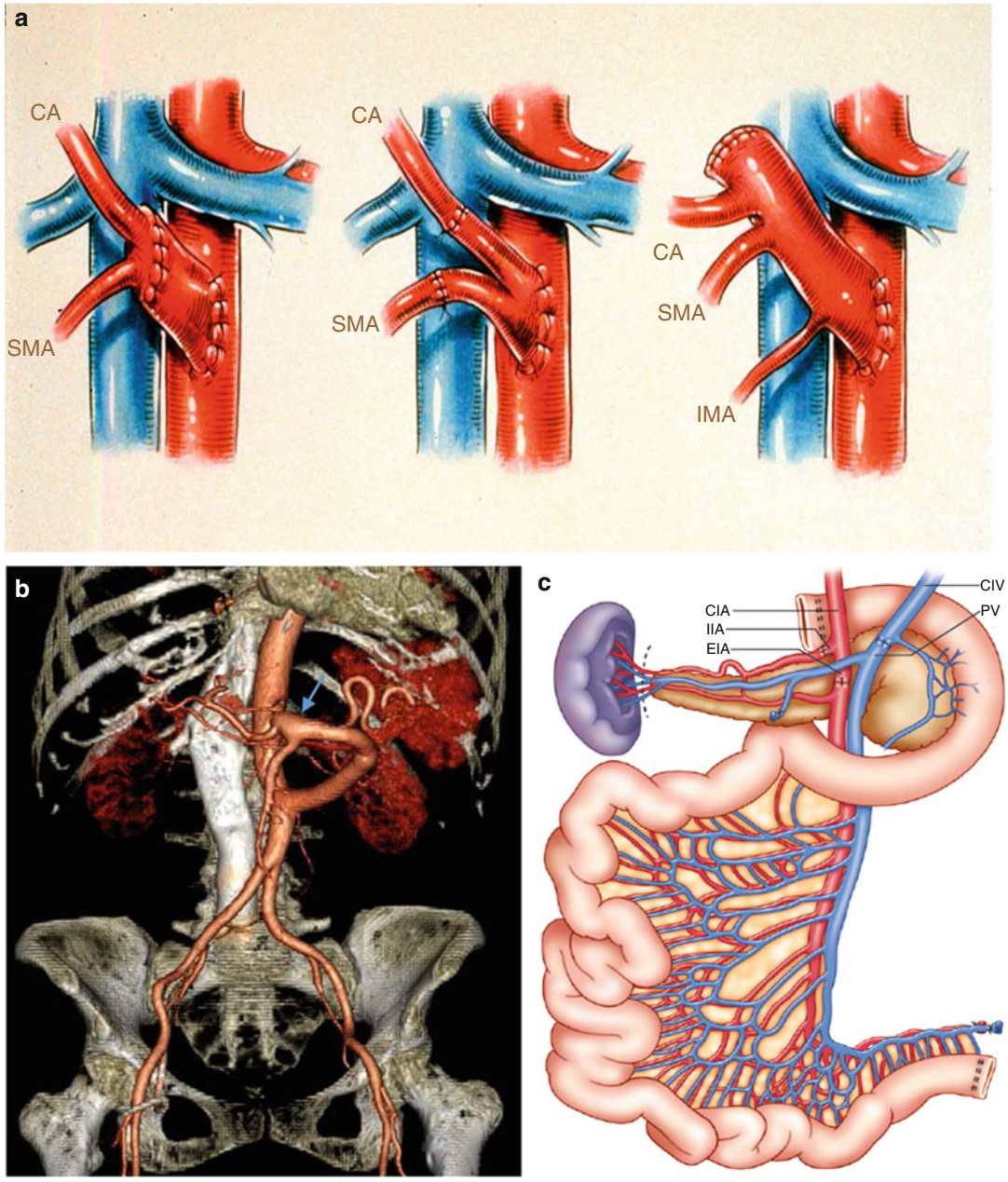

Fig. 5 (**a**) The different types of vascular reconstruction of the composite visceral allograft. CA: celiac artery, SMA: superior mesenteric artery, IMA: inferior mesenteric artery. (**b**) A 3-D reconstruction of CT angiogram in a multivisceral recipient. Note the Carrel-patch reconstruction (arrow) that was performed on the back table containing both the celiac and superior mesenteric origin. (**c**) En bloc retrieval of the intestine and pancreas with back table vascular reconstruction. Splenectomy and ligation of the bile duct stump are also performed as part of the back-table procedure. Placement of an interposition vein graft is not needed. CIA: common iliac artery, CIV: common iliac vein, IIA: internal iliac artery, EIA: external iliac artery, PV: portal vein. (Adapted with permission from Abu-Elmagd, K., Bond, G., Reyes, J. et al. Intestinal transplantation: a coming of age. Adv Surg. 2002; 36: 65–101)

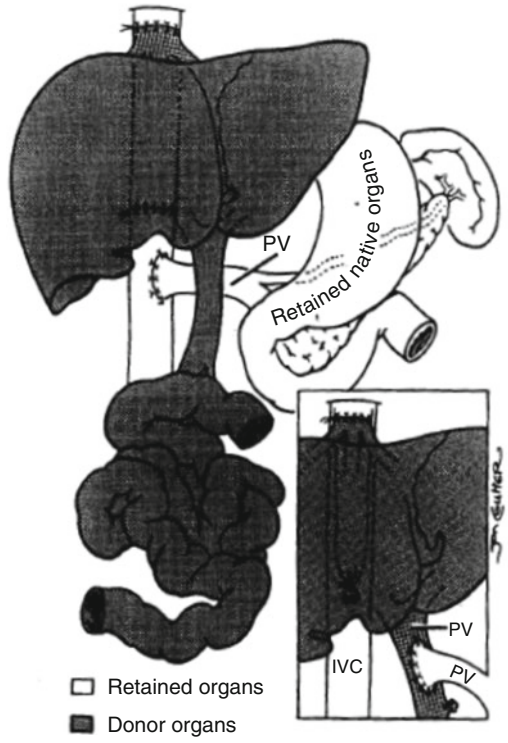

Fig. 6 Drainage of the venous outflow of the retained native viscera in liver-intestinal recipients into their inferior vena cava (IVC) by portocaval shunt. The previously adopted porto-portal shunt (inset) is no longer practiced at our center. (Used with permission of Starzl TE, Todo S, Tzakis A, et al. The many faces of multivisceral transplantation. Surg Gynecol Obstet 1991;172:335–44. *Surgery, Gynecology, & Obstetrics* is now known as the *Journal of the American College of Surgeons*; Buchman et al. 2003)

As part of the two-way immune interaction, the incidence of graft-versus-host disease (GVHD) in isolated intestinal transplantation is reported to be less than 10% (Clouse et al. 2017). Higher rates are seen in composite visceral allograft recipients, particularly in children with immunodeficiency, and in those who had splenectomy or were pretreated with antilymphocyte-depleting agents (Abu-Elmagd et al. 2017). The disease commonly involves the recipient's skin and gastrointestinal tract and is confirmed with histopathologic examination of the affected organ(s) and detection of circulating donor cells in the peripheral blood of the recipient.

Management of infectious complications has gradually been enhanced as the result of cumulative clinical experience, advances in molecular diagnostic techniques, and availability of new antimicrobial drugs. The clinical availability of the quantitative competitive polymerase chain reaction (PCR) assay triggered serial monitoring of Epstein-Barr virus (EBV) and cytomegalovirus (CMV) load in peripheral blood. Treatment strategies include prophylactic antibiotics, preemptive therapy of EBV and CMV viremia, and active treatment of bacterial and fungal infections. These management protocols, along with minimization of posttransplant immunosuppression, have significantly reduced risk and mortality of PTLD, CMV, and microbial infections.

The ability to restore nutritional autonomy and graft function is the second most important indicator of successful visceral transplantation after survival. Assessment of graft function is accomplished through careful serial clinical, biochemical, and nutritional assessments (Abu-Elmagd et al. 2001). When transplantation is effective, most recipients tolerate oral feeding within the first 2 weeks of surgery. Within 4 weeks, PN and supplemental IV fluids are commonly discontinued with achievement of full nutritional autonomy. The failure to achieve full recovery of GI function, particularly gut motility and fat absorption, may be the result of denervation and lymphatic disruption of the intestinal allograft, respectively (Rovara et al. 2003).

Bacterial and fungal overgrowth is also a common finding in the intestinal allografts brought about by change in the ecology of the intestinal flora. Proposed mechanisms for altered gut microbiota include surgical manipulations, absence of the ileocecal valve, disruption of the intestinal lymphatics, impaired host defenses due to heavy immunosuppression, gut dysmotility, preservation injury, rejection, or PTLD (Abu-Elmagd et al. 2001). Further study is needed to plot dynamic changes in the intestinal allograft microbial ecology and its potential influence on allograft graft function, rejection, and survival (Abu-Elmagd 2015).

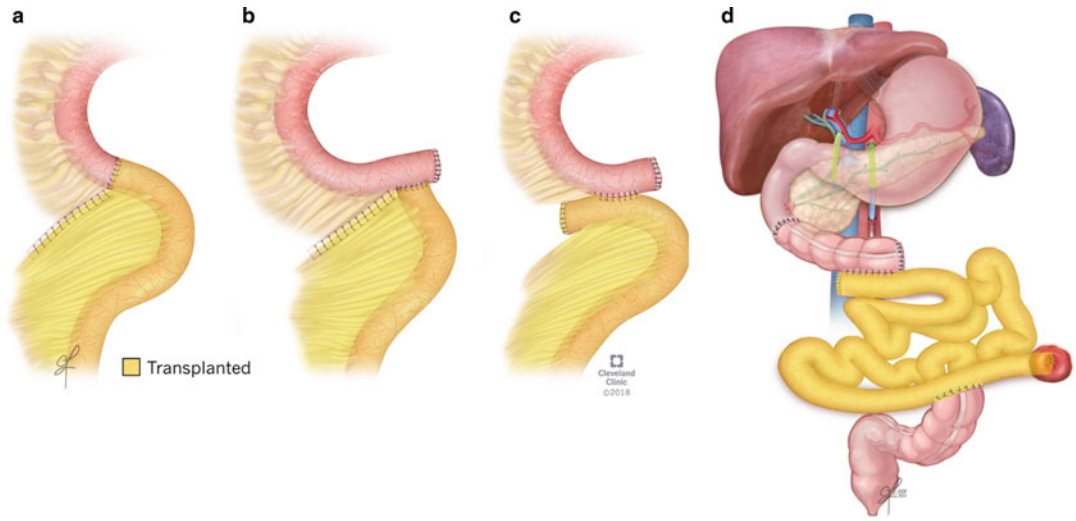

Fig. 7 Gastrointestinal Reconstruction. Proximal allograft jejunum is anastomosed to the retained short segment of native jejunum in an (**a**) end-to-end, (**b**) end-to-side, or (**c**) side-to-side fashion. Foregut reconstruction with (**d**) interposition segment of the native colon. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography. Copyright 2009–2018. All Rights Reserved; Buchman et al. 2003)

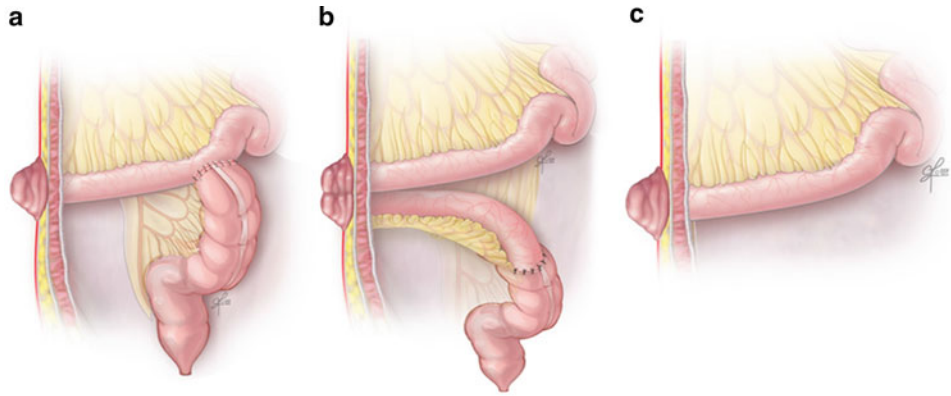

Fig. 8 Hindgut reconstruction with creation of a (**a**) chimney ileostomy, (**b**) simple loop ileostomy, or (**c**) end ileostomy. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography. Copyright 2009–2018. All Rights Reserved; Buchman et al. 2003)

Long-Term Outcomes

The survival outcome of visceral transplantation has significantly improved over the last few decades. According to the Intestinal Transplant Registry (ITR), there is compelling evidence that the 5-year patient and graft survival has significantly improved (Fig. 9a) (Grant et al. 2015). Similar results have been documented by the Pittsburgh largest single center experience with the longest follow-up worldwide (Fig. 9b) (Abu-Elmagd et al. 2009b). Such an improvement in survival outcome can be partially due to innovative surgical techniques, improved postoperative care, and novel immunosuppressive protocols (Fig. 9b, c) (Abu-Elmagd et al. 2009a). Equally impressive is the Pittsburgh long-term outcome beyond the post-transplant 5 year landmark with

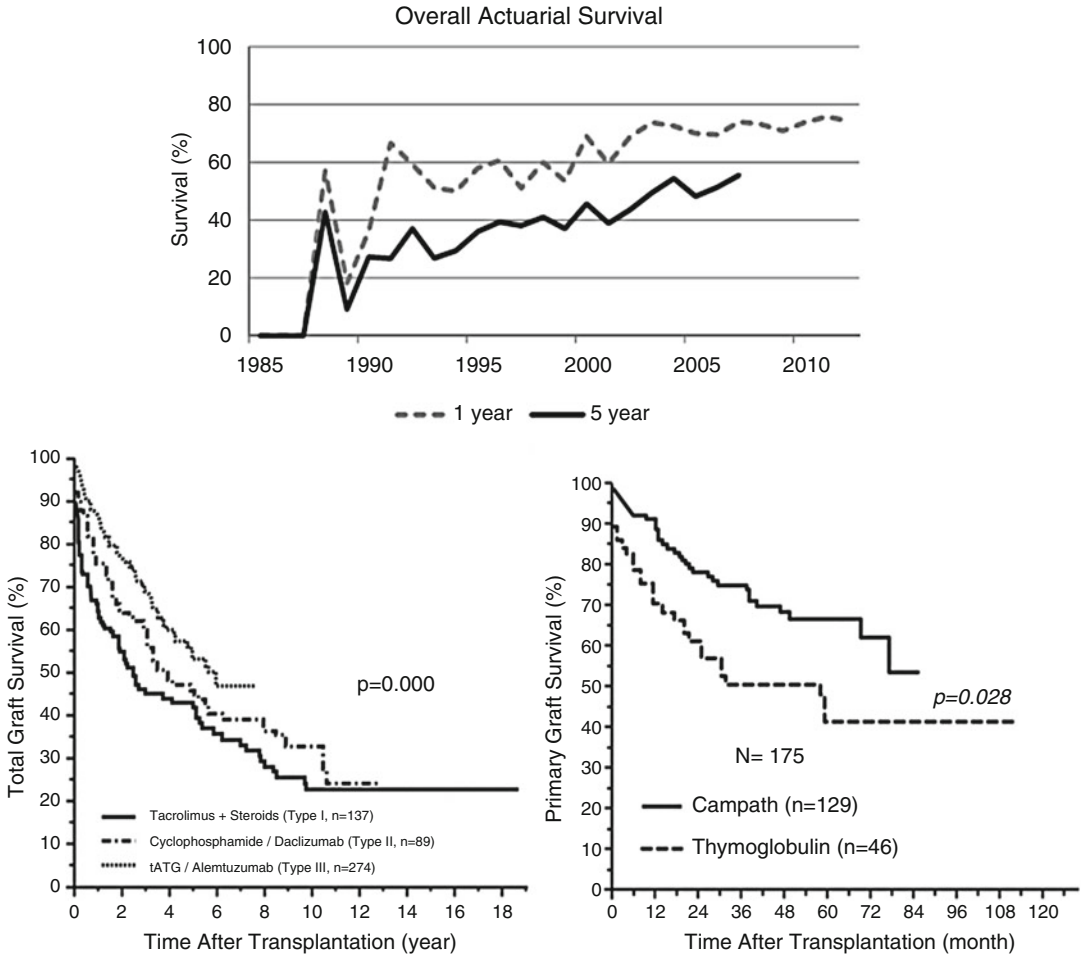

Fig. 9 (**a**) A times series analysis of the 1- and 5-year actuarial graft survival shows significant improvement over time ($p < 0.001$). (Used with permission of Grant D, Abu-Elmagd K, Masariegos G, et al. Intestinal transplant registry report: Global activity and trends. Am J Transplant 2015;15:210–19); (**b**) improvement of visceral allograft survival according to the type of immunosuppression. (Used with permission of Abu-Elmagd KM, Costa G, Bond GJ, et al. Five hundred intestinal and multivisceral transplantations at a single center: major advances with new challenges. Ann Surg 2009;250(4):567–81); and (**c**) better graft survival in patients pretreated with alemtuzumab (Campath-1H) compared to those pretreated with antithymocyte globulin (thymoglobulin) (Used with permission of Abu-Elmagd KM, Costa G, Bond GJ, et al. A decade of experience with a single dose of rabbit antithymocyte globulin or alemtuzumab pretreatment for intestinal and multivisceral transplantation. Clin Transpl 2012:155–66)

a patient survival rate of 75% at 10 years and 61% at 15 years with a respective graft survival of 59% and 50% (Fig. 10) (Abu-Elmagd et al. 2012). The study also documented the significant risk factors that affect long-term survival as shown in Table 3.

Nutritional autonomy following visceral transplantation is defined as freedom from intravenous nutrition and fluid supplementation with the goal of removing central venous access and eliminating associated complications to thereby restore a more physiologic way of life. With a mean follow up of 10 +/− 4 years, full nutritional autonomy was achievable in 90% of visceral transplant survivors as reported in the Pittsburgh long-term outcome study (Fig. 11a) with a significant and sustained improvement in body mass index (BMI) among the adult population (Fig. 11b). All

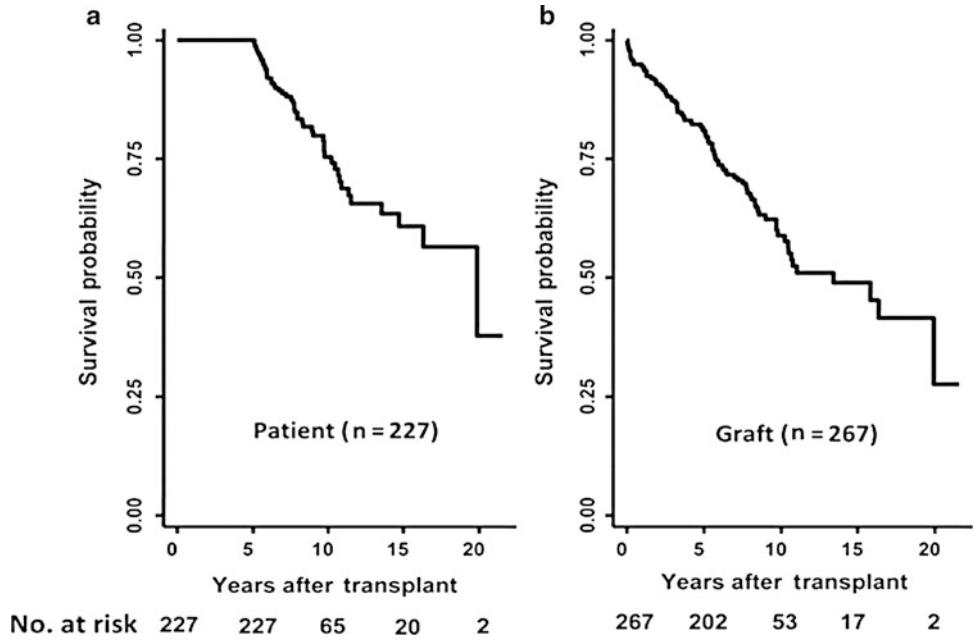

Fig. 10 Kaplan-Meier survival curves for the 5-year conditional patient (**a**) and graft (**b**) survival after visceral transplantation. (From Abu-Elmagd KM, Kosmach-Park B, Costa G, et al. Long-term survival, nutritional autonomy, and quality of life after intestinal and multivisceral transplantation. Ann Surg 2012;256(3):494–508, with permission)

Table 3 Long-Term Patient Survival Risk Factors and Predictors of Graft Failure

	P	Hazard ratio	95% confidence interval
Patient			
Lack of social support	0.000	6.132	3.370–11.160
Rejection ≤90 day	0.016	2.363	1.172–4.765
Female recipient	0.025	1.992	1.089–3.646
Recipient age ≥ 20 yr	0.025	2.014	1.093–3.711
Retransplantation	0.026	2.053	1.089–3.873
No preconditioning	0.046	2.013	1.013–4.997
Graft			
Liver-free allograft	0.000	3.224	2.026–5.132
Splenectomy	0.001	2.212	1.396–3.506
HLA mismatch	0.040	1.258	1.011–1.565
Rejection ≤90 day	0.046	1.601	1.008–2.541
PTLD	0.085	1.638	0.934–20,872

children experienced normal growth except a few who required growth hormone.

With improved survival and nutrition outcome, quality of life has become one of the primary therapeutic end points of visceral transplantation. A few scattered reports have been published within the last 20 years among both children and adults (Sudan et al. 2000, 2002; Ngo et al. 2011; Cameron et al. 2002; Pironi et al. 2006, 2012; Golfieri et al. 2010; O'Keefe et al. 2007). Studies among children undergoing visceral transplantation demonstrated physical and psychosocial functions similar to healthy normal children (Sudan et al. 2002; Ngo et al. 2011). However, the parental proxy assessments were different with lower functional responses in certain

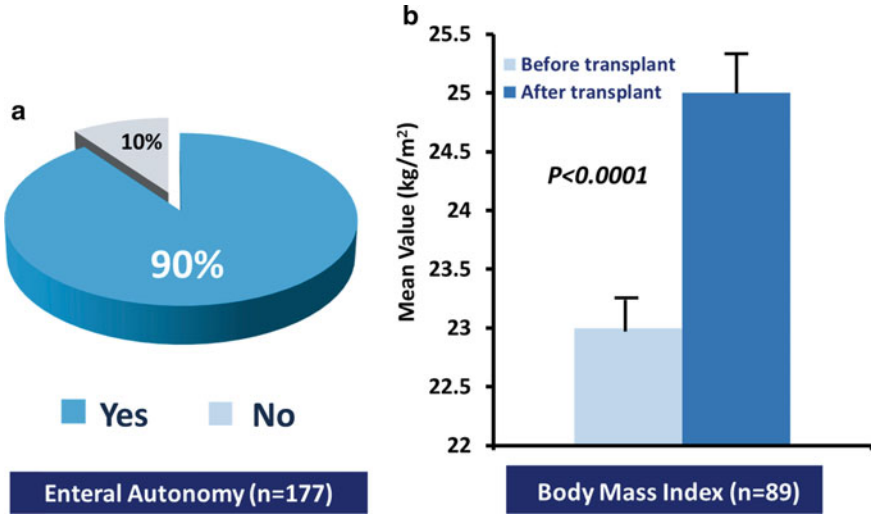

Fig. 11 Nutritional autonomy after visceral transplantation. (**a**) Achievement of enteric autonomy defined by freedom from intravenous nutrition and fluid supplement. (**b**) Body mass index before and after transplantation. (From Abu-Elmagd, K.M., Kosmach-Park, B., Costa, G. et al. Long-term survival, nutritional autonomy, and quality of life after intestinal and multivisceral transplantation. Ann Surg. 2012; 256: 494–508, with permission)

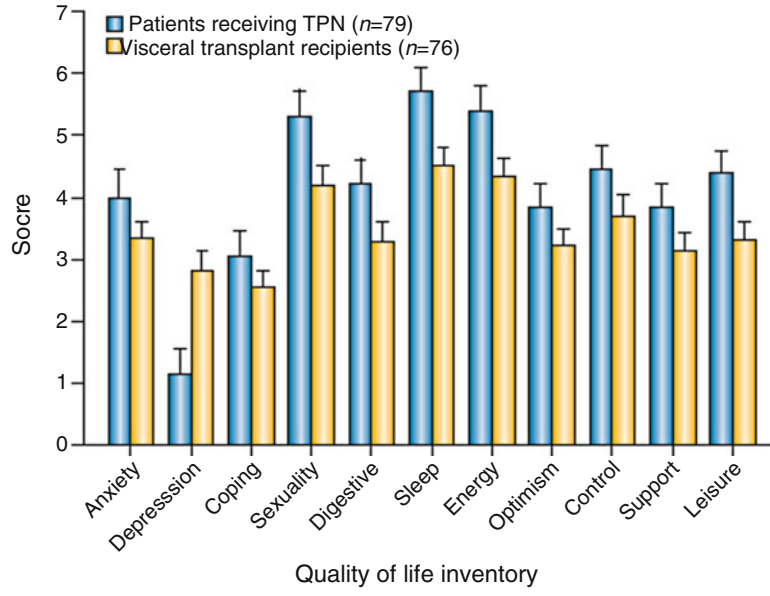

Fig. 12 Reversal of the depressed effect of PN on most quality of life domains, except depression, after visceral transplantation. (From Abu-Elmagd, K.M., Kosmach-Park, B., Costa, G. et al. Long-term survival, nutritional autonomy, and quality of life after intestinal and multivisceral transplantation. *Ann Surg.* 2012; 256: 494–508, with permission)

categories than that given by transplanted children. In addition, lower values in the school functioning subcategories and psychological health summary score were reported compared with healthy children (Ngo et al. 2011). In adults, most published studies on health-related quality of life (HRQOL) have demonstrated improvement in all of the domains except for depression, with better rehabilitative indices than PN (Fig. 12) (Abu-Elmagd et al. 2012).

Socioeconomic milestones have also been used to assess the level of rehabilitation achieved with visceral transplantation in all age groups (Abu-Elmagd et al. 2012). A high education score was reported with sustained cognitive, psychosocial, and physical functions. In addition, the

ability to create a nuclear family along with high Lansky and Karnofsky performance scores is demonstrated and comprehensively reported (Abu-Elmagd et al. 2012). The data have also been in favor of early consideration for visceral transplantation to further improve quality of life by reducing the risk of organic brain-dysfunction-related morbidities associated with brain atrophy, cerebral vascular insufficiency, micronutrient deficiencies, trace element toxicities, and liver-failure (Idoate et al. 1999; Dekaban 1978; El-Tatawy et al. 1983; Kawakubo et al. 1994). Accordingly, early consideration of transplantation is strongly recommended for patients with irreversible gut failure who are not suitable candidates for autologous gut rehabilitation.

Conclusion

Visceral transplantation has become the definitive treatment for patients with end-stage intestinal failure and life-threatening complications of PN. Advances in surgical technique, immunosuppressive therapy, early identification, and treatment of infection and gains in center experience have led to improved patient and graft survival. Management of the chronic complications of long-term immunosuppression including hypertension, diabetes, renal failure, osteoporosis, and other associated morbid events is important to further successful outcomes. Despite successful treatment, morbidity of long-term immunosuppression remains detrimental to patient care and overall health. Accordingly, efforts to achieve transplant tolerance with drug-free allograft acceptance are essential along with early patient referral and listing for the long-term therapeutic efficacy of intestinal and multivisceral transplantation.

Cross-References

- ▶ Causes of Short Bowel Syndrome in Adults
- ▶ Modern Parenteral Nutrition
- ▶ Psychosocial Issues in Intestinal Transplantation
- ▶ Recent Evolution of Gut Rehabilitation

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Intestinal and Multivisceral Transplantation: The Operation

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Abstract

Intestinal transplant remains the most complex, expensive, and uncommon transplant among all the solid organs. However, given its 1-year survival is now as high as other solid organs, it is no longer considered an experimental procedure. Recent advances in patient and graft survival, in part, are due to the refinement of the surgical techniques. Advances in patient and donor selection and better understanding of immunological and infectious complications have also contributed to improved outcomes. Given intestinal failure is often found in the presence of other organ damage, the intestine is the core of what has most recently been called *visceral transplantation*. A combination of classic and newer techniques of visceral transplantation and its most common variations will be described. This chapter reflects solutions and evolvement in the realm of visceral transplantation based on hundreds of cases over more than 10 years.

Keywords

Intestinal transplant · Visceral transplantation · Multivisceral transplant · Modified multivisceral transplant · Colon transplant · Abdominal wall transplant · Hybrid ostomy · Intestinal failure · Portal mesenteric thrombosis · Short bowel syndrome · Motility disorder

Introduction

Intestinal transplant is no longer an experimental procedure as its 1-year survival is as high as other solid organs. Part of this success is due to refinement of surgical techniques, advances in patient and donor selection, and better understanding of immunological and infectious complications. It is still the most complex, expensive, and uncommon transplant among all the solid organs; due to these reasons, it is only performed in a few centers around the globe.

Intestinal failure is often found in the presence of other organ damage requiring the transplant of multiple viscera. The scope of this chapter is to describe the surgical techniques of visceral transplantation and its most common variations. The intestine is the core of what has most recently been called visceral transplantation. Immunologically, we could divide visceral transplantation into liver-inclusive and liver-exclusive grafts. Although, there is a continuous discussion about nomenclature, for didactic purposes we will describe here the three most common variations of visceral transplantation: isolated intestine (intestine-colon), modified multivisceral, and multivisceral transplantation (Bhamidimarri et al. 2014) (Fig. 1).

Isolated Intestinal Transplant (Intestine-Colon)

Isolated intestinal transplant, or intestine-colon, is a procedure currently indicated when patients develop life-threatening complications of parenteral nutrition. The main indication is short bowel syndrome. Most recent series demonstrates excellent survival; hence, it is becoming the treatment of choice for intestinal failure (Beduschi et al. 2015, 1). This procedure is selected when the liver, pancreatic, and gastric functions are preserved.

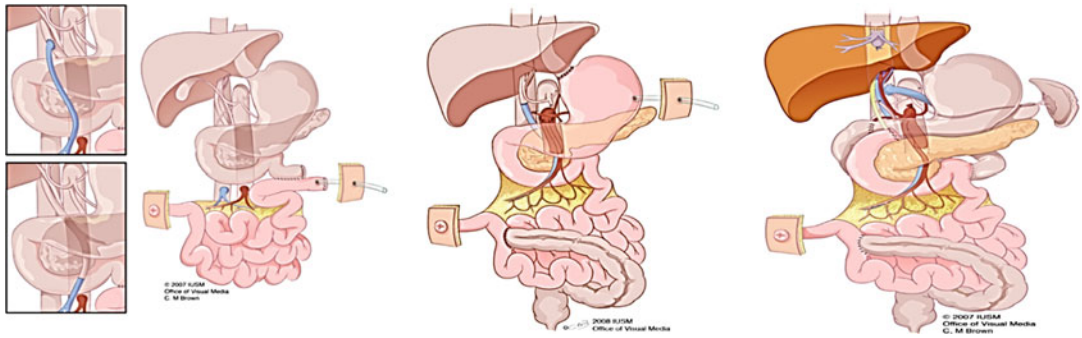

Fig. 1 Main types of visceral transplant: isolated intestine, modified multivisceral, and multivisceral

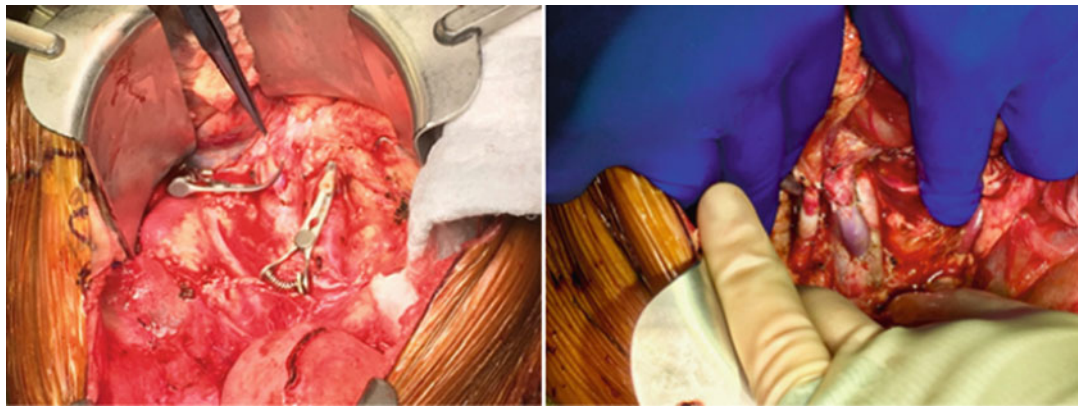

Fig. 2 (**a**) Dissection of vena cava and aorta, (**b**) Vascular grafts were anastomosed to vena cava and aorta

Surgical Technique

In general, a xyphopubic midline incision with the use of a "Bookwalter" type retractor is the preferred approach. The presence of multiples adhesions, enterocutaneous fistulas, and ostomies are not uncommon, making the dissection sometimes difficult and labored. Special attention and careful dissection are fundamental to avoid injury to the duodenum, bladder, and ureters. They may be very attached to other structures, making a distorted anatomy a common finding.

After the diseased native intestine is removed, it is time to think about the type of vascular reconstruction to be performed. This depends on the native disease, size and quality of the vessels, and surgeon's preference. The mesenteric vessels can be placed in a heterotopic position, to aorta and cava, and in an orthotopic position, to superior mesenteric artery and vein. Basically, if the patient lost the intestine due to vascular disease, a heterotopic reconstruction is the most logical choice. Also, if the patient presents some degree of liver fibrosis, mild portal hypertension, or some congestion of the liver, systemic drainage is a better and safer option for the intestinal graft. For the other indications, orthotopic placement of the vessels is preferred. A combination of both can be done as well.

Heterotopic or Systemic Drainage (Fig. 2a, b)

Infrarenal aorta and vena cava are dissected. In the aorta dissection, the superior limit is the left renal vein. Inferiorly, the level of inferior mesenteric artery or just below should be sufficient. Similar dissection is carried on at the vena cava. The gonadal vein may be ligated if at the level of the anastomosis. Space should be adequate to allow a small *satinsky* clamp to be applied.

Sizeable lymphatics should be divided between ties to avoid chylous ascites. Before the aorta and/or cava clamping, 50–100 U/kg of heparin (maximum 5000 U) is given. The use of extension vascular grafts is preferred to decrease the clamping time of the main vessels, facilitate the operation, and at the same time, to make it safer. Donor iliac vein is usually used as vein graft, and donor carotid artery is thought to be the best match for the superior mesenteric artery. In case it is not available, donor iliac artery can be used. After the anastomosis of the extension grafts, small clamps are applied individually, and the *satinsky* clamps are removed from the aorta and vena cava. At this point, the intestinal graft is brought to the surgical field, and attention is turned to the length of the vessels. If they are too long, there is an increased risk of kinking and further vascular thrombosis. First anastomosis is the arterial, and it is performed in a parachuting fashion. Extra attention should be paid in the venous anastomosis. Correct orientation is fundamental to avoid problems. Very often it is difficult to determine which is left and right in the superior mesenteric vein in the graft. For this reason, it is highly recommended to have both sides marked with a pen or small sutures placed during the donor operation when the graft is being harvested to prevent a mistake. Once right and left is defined, the anastomosis is performed in a standard fashion. When clamps are removed, it is uncommon to have hemodynamic instability or any major bleeding because most of the dissection of the graft is carried on in the warm phase in the donor. Intestinal graft should perfuse quickly, and a beautiful pink color should be observed. Any sign of venous congestion should be promptly evaluated and usually requires repositioning of the graft to correct an outflow obstruction due to torsion of the vein. Vein graft should be very soft to digital compression; if not, a problem in the anastomosis should be ruled out. Careful manipulation of the graft is essential after reperfusion to avoid traction and injury to the anastomoses.

Orthotopic or Portal Drainage (Fig. 3)

The dissection for the orthotopic drainage requires more time, and it is more labored, but it is preferred whenever possible. Dissection of the superior mesenteric vein is performed almost to the level of the confluence to the splenic vein. Usually the first jejunal branches of the vein and the artery can be preserved. Venous branches from the uncinate process of the pancreas may need to be tied to release the vein and to achieve a more anatomical position for the anastomoses. The need for extension vascular grafts is defined by the length of the vessels in the graft, depending mainly if the pancreas was also harvested or not and the position of the vessels. You will not always find the superior mesenteric vein on the right side and superior mesenteric artery immediately on the left. They can have a more vertical position to each other. The use of extension vascular grafts can correct this position allowing a proper angle to the anastomoses. Selection of the extension grafts and the use of heparin were mentioned above and follow the same principle. At this point, the intestinal graft is brought to the field, and anastomoses are performed in a standard fashion. Artery is done first, and vein follows after careful identification of the right and left side. Reperfusion should occur in an uneventful way, and the graft should not present any signs of congestion.

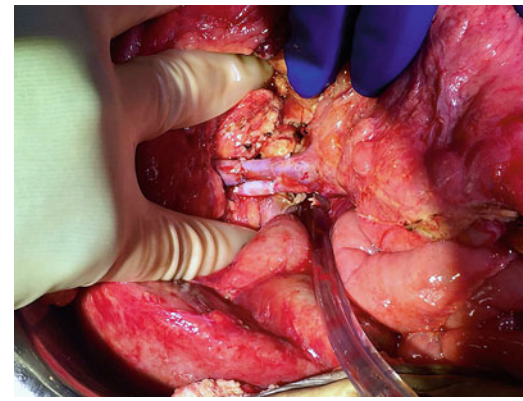

Fig. 3 In this case, extension graft was placed only in the superior mesenteric artery

Proximal Reconstruction and Gastrostomy

A jejunum to jejunum anastomosis is the most common proximal reconstruction. Sometimes,

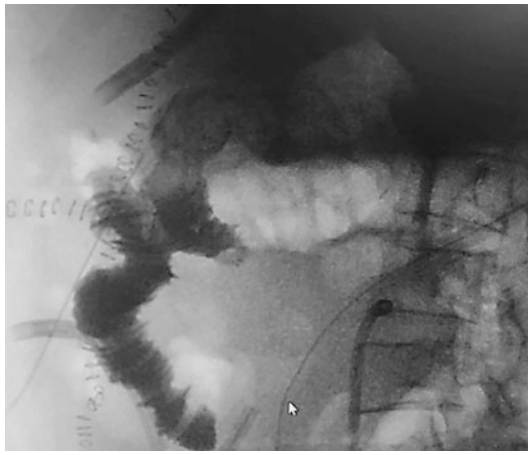

Fig. 4 Duodeno-jejunum anastomose performed in the second portion of duodenum

duodeno-jejunum (Fig. 4) or even gastro-jejunum is required depending of the native anatomy of the recipient. The anastomosis is performed hand sewing, in two layers, 10–15 cm from the Treitz ligament if possible. This extra length will allow placing a jejunostomy in case the graft has to be removed for any circumstance.

Gastrostomies are reserved for the patients with food aversion or previous gastrostomies. Most of the patients leave the operating room with a naso-jejunal tube.

Multivisceral Transplant

Multivisceral transplant includes the transplant of the liver, stomach, pancreas, small bowel, and colon. It is a rare procedure, requiring extra expertise and structure of the hospital. To be a successful surgical team, anesthesia and critical care have to collaborate. It is the most complex operation a human being can have, and for this reason, not only surgical steps will be discussed but also a few anesthetics and perioperative considerations.

Anesthetic Considerations

At least two good central venous accesses should be obtained before starting the operation. Other than central access, good and sizable peripheral veins should be cannulated as well. Two arterial lines, central venous pressure, and transesophageal echocardiogram are part of the hemodynamic monitoring. Usually 20–40 units of pack red blood cells, fresh frozen plasma, and platelets should be placed on hold. If a patient develops coagulopathy after reperfusion, cryoprecipitate may be necessary. Judicial use of pressors during the explant will decrease the need for volume replacement. Decreasing the venous pressure will decrease the blood loss from varices.

Special attention should be given to the massive transfusion of plasma, platelets, and cryoprecipitate directly into the heart with the rapid infuser. These patients are hypercoagulable at baseline, and there is an increased risk of development of cardiac thrombus. An alternative is to transfuse those products separately using the peripheral access or into a femoral line, avoiding direct contact with the valve trabeculae in the heart and intracardiac thrombus formation.

After reperfusion, requirement of volume will increase substantially. Very often, a large amount of fluid shifts to the third space and into the intestine. Most likely this is the effect of the reperfusion syndrome and may last more than 24 h.

Surgical Technique

A xyphopubic midline incision with extension to the right should be performed. Sometimes, due to the size of the spleen, an extension to the left (cruciate incision) may be necessary. Huge varices may be noted in the skin, and major bleeding with mortality even before entering the abdominal cavity has been described.

Exenteration

After inspection of the cavity and control of the varices in the abdominal wall, the dissection starts mobilizing the right colon and small intestine from the retroperitoneum. Many collaterals will be found in this normally "avascular plan." Combination of electrocautery, ties, and bipolar vessel sealing device is used to dissect and achieve hemostasis. Once the intestine is mobilized and

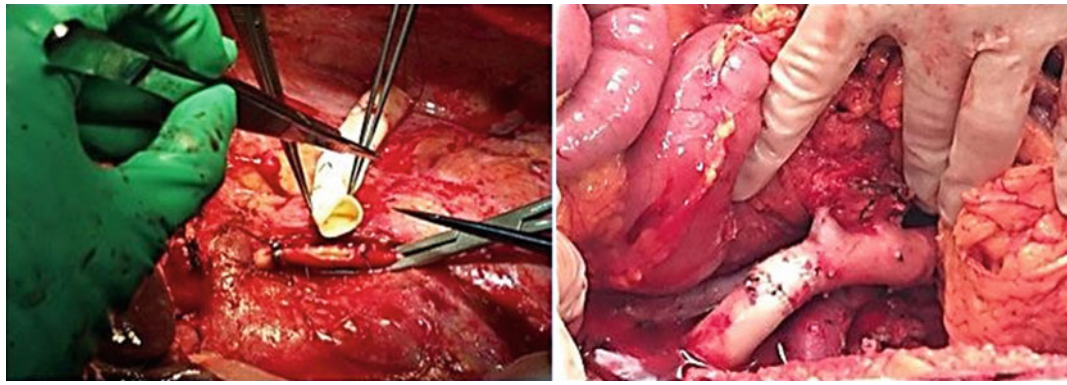

Fig. 5 Aorta clamped and jump graft being anastomosed. Aortic graft after reperfusion

retroperitoneum is exposed up to left renal vein, a right and transverse colectomy is performed, dividing the colon at the level of the splenic flexure. The next step is to remove the small bowel. Jejunum is divided with linear stapler just after the ligament of Treitz, and straight vascular clamps are placed in the mesentery. After the entire intestine is removed, the mesentery is oversewn.

At this point, anatomy and previous surgeries will define the best strategy. If possible, the pancreas is encircled, clamped, and divided at the level of the body. This approach exposes the celiac trunk and the superior mesenteric artery, which are subsequently tied. Subsequently, the spleen and the pancreas should be mobilized from the retroperitoneum in a plain above the left adrenal gland. Kocher maneuver is performed. Short gastric vessels should be divided from the spleen, and using linear stapler, the stomach is divided preserving a cuff for the future anastomosis. The spleen and the tail of the pancreas are removed. The liver hilum is divided between clamps as well, and piggyback technique is performed. The liver, head of the pancreas, and duodenum are removed.

The infrarenal aorta is fully exposed and dissected, and a vessels' loop is placed around the inferior mesenteric artery. The aorta is clamped, and the artery is incised with a number 11 blade. An opening is created using an aortic punch. Anastomosis between a short segment of thoracic aorta from the donor and the infrarenal aorta is performed using running prolene sutures (Fig. 4). The aortic conduit is clamped, and the clamp from the aorta is released. The anesthesia team should be informed prior to the removal of the aortic clamp because usually a drop of more than 40 mmHg points in the systolic pressure may be temporally observed.

Embolization of the celiac artery and superior mesenteric artery immediately before the transplant may facilitate the exenteration of native organs, decreasing the blood loss and requirement of transfusions as described by Pirene's group recently (Ceulemans et al. 2015).

Implant

A common opening among the hepatic veins is created. The multivisceral graft is brought to the table, and an anastomosis between the superior vena cava of the graft and the hepatic veins of the recipient is performed in a running fashion with prolene sutures. Graft is irrigated with 3 L of a solution with albumin 10% in room temperature or flushed with blood before releasing the venous clamp. Anastomosis between the aortic conduit and the aorta of the donor is performed in a running fashion (Fig. 5). At this point, graft is ready to be reperfused. Total anhepatic phase is usually less than 1 h.

Reperfusion is the most critical part of this operation, and the entire team should be ready for adverse events. Blood pressure should be preferably above 120 mmHg of systolic. Potassium must be low. Syringes with sodium bicarbonate, calcium, insulin, magnesium, and vasoactive drugs must be ready to be used in case needed. Liters of warm

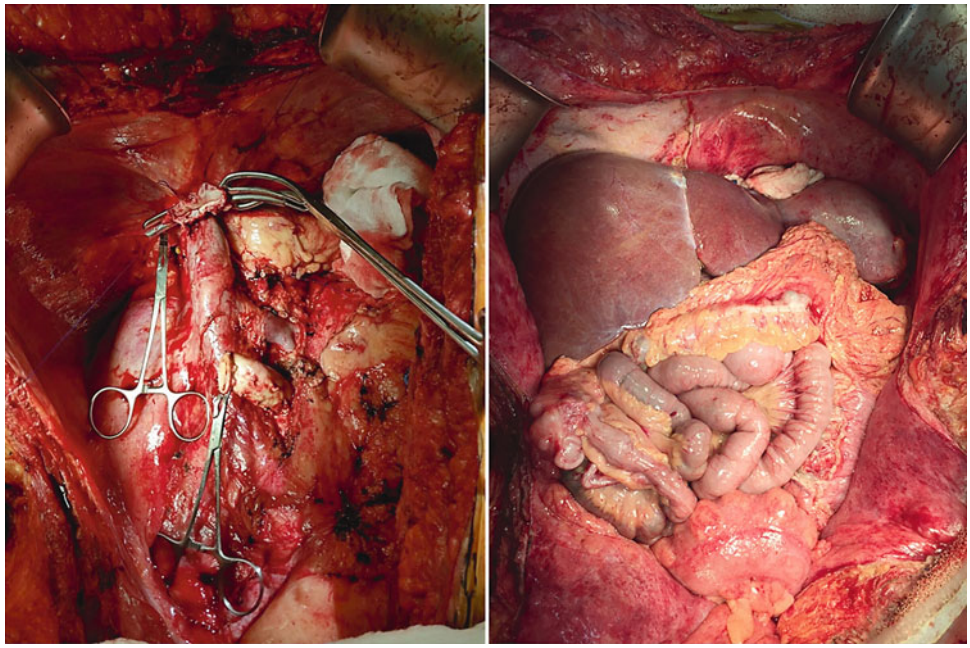

Fig. 6 Abdominal cavity empty with the aortic graft in place and then after reperfusion

irrigation must be available. Patient's heart will receive a load of potassium from the cold preservation solution. After the clamps are removed, patient will behave as if they are losing blood. Blood, cold and full of potassium from the preservation solution, has to fill the entire multivisceral graft before returning to the heart. Arrhythmias and hemodynamic instability are not uncommon. Major problems will be seen in the first 10 min after reperfusion. Coagulopathy after reperfusion is common and should be corrected with a combination of platelets, plasma, and cryoprecipitate. Further transfusions will be based on the thromboelastogram findings (Fig. 6).

After hemostasis is accomplished, a gastric-gastric anastomosis is performed in two layers. Once the posterior wall is finished, a nasogastric tube and a naso-enteric tube are placed, and the anterior layer is completed. A Nissen fundoplication is the final step of the upper anastomosis (Fig. 7). Gastric tube is rarely performed. Pyloroplasty is routinely done. A colon-colon anastomosis is the final step of the operation and should be done preferentially end-to-end or end-to-side fashion**.** Side to side seems to be safer, although it makes the colonoscopies technically very challenging**.** Ostomies are no longer performed in patients with preserved native colon in some centers due to the low incidence of rejection in multivisceral patients (Beduschi et al. 2015, 2). All the spaces in the mesentery between the anastomosis should be closed to prevent volvulus. Primary closure of the fascia is achieved in most of the patients with splanchnic thrombosis, but there is need for biological mesh in most of the short bowel patients.

Sometimes patients can develop severe coagulopathy, and the surgery may not be finished at one time. Packing with lap sponges and closing the skin only is an alternative to stabilize the patient in the critical care unit. In these cases, the colonic anastomosis and final closure are performed in 24 or 48 h or as soon patient becomes hemodynamically stable.

Postoperative Period

The initial post operator period of a multivisceral transplant patient may be very challenging.

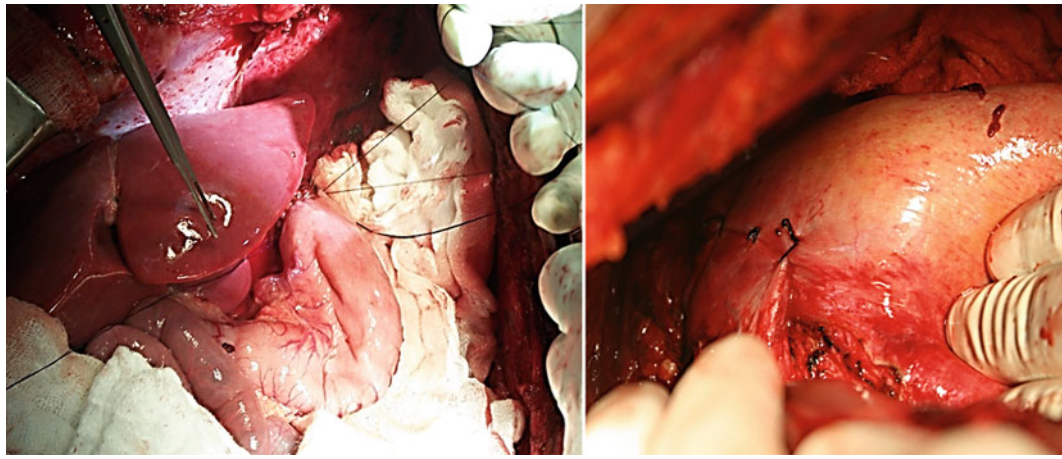

Fig. 7 Gastric-gastric anastomose and Nissen fundoplication

Surgical trauma is enormous. Massive transfusions in the operating room are not uncommon. Sometimes substantial blood transfusions continue in the ICU. Large amount of fluids are required in the first 24–48 h. Nasogastric tube is kept for 7–10 days, then diet is started, and parenteral nutritional weaned off as oral intake improves. Induction with anti-lymphocyte preparations is almost universal among centers, and maintenance varies around the use of tacrolimus and a second agent. Steroids are usually discontinued a few months after transplant. Lower endoscopies are performed according to the center's preference. If no ostomy is placed, as is the new norm in some centers, the first scope is performed after 3 weeks and/or if symptoms of rejection occur. Follow-up with citrulline, immunoglobulin levels, chimerism, and donor-specific antibodies is performed for all the patients routinely.

Multivisceral Backup Concept

One of indications for multivisceral transplantation is end-stage liver disease with diffuse portomesenteric thrombosis. For patients with very extensive thrombosis, a liver transplant may not be possible, and a multivisceral transplant is the ultimate option. Once all the minimally invasive options to reestablish adequate portal flow are exhausted, a multivisceral transplant is considered. For some patients with Grade 4 thrombosis though, a liver transplant still may be performed (Vianna et al. 2012). Triple phase CT scan is carefully evaluated. In patients with multiple abdominal surgeries (hostile abdomens), or if there is a possibility to restore the portal flow utilizing low dissection of the main portal vein combined with thromboendovenectomy or a venous jump graft to a mesenteric branch, the patient is listed for a multivisceral backup. In this way, a multivisceral graft is available in the operating room during the transplant. Patients listed for a multivisceral backup should be anticoagulated to avoid worsening of the thrombosis.

The concept is simple. The candidate is listed for a regular multivisceral transplant (stomach, pancreas, liver, small bowel, and colon). Once a donor becomes available, the organs are harvested "en block" with standard techniques. Dissection in the recipient starts a little earlier than usual and differs from a standard multivisceral.

The initial dissection is very similar to a liver transplant. After mobilization of the liver, attention is turned to the hilum. Careful dissection of the hepatic artery is performed. The artery is dissected and individualized from the adjacent tissues but should not be tied at this point. Bile duct is identified and divided between sutures. Portal vein should be carefully skeletonized. Hepatic artery should be very mobile at this point,

especially after the ligation of the gastroduodenal artery. A vein retractor should medially retract the hepatic artery giving full access to the portal vein. After the transection of the portal vein, a meticulous low dissection of the portal vein combined with thromboendovenectomy is performed. Dissection of the branches of the superior mesenteric vein in the mesenteric root can also be attempted. Collaterals or the inferior mesenteric vein are also viable options. All these techniques have been described elsewhere.

Preserving the hepatic artery during the dissection of the portal vein avoids prolonged and unnecessary anhepatic phase leading to early coagulopathy and metabolic acidosis. After careful evaluation of all the possible alternatives to restore portal flow, decision is made to proceed with a liver alone or to switch to a multivisceral transplant. The rationale for using this approach is to offer all the possibilities to the candidate and also to be able to perform low dissection and thromboendovenectomy in an aggressive way and still be able to rescue the situation if uncontrollable bleeding occurs or if no flow is achieved utilizing the portomesenteric system.

If the decision is to proceed with a liver only, the organs are separated in the backbench, and the pancreas is transplanted in another recipient. The pancreas is allocated in advance as backup for another recipient. Logistically, it works better if the backup patient is in the same center or in a near center in order to minimize ischemic times.

Modified Multivisceral Transplant

Modified multivisceral transplant includes the transplant of the stomach, pancreas, small bowel, and colon. By far, the most common indication is pandysmotility of the gastrointestinal tract with preserved liver function. It is a technically demanding operation with unique features.

Explant

Resection of the stomach, pancreas, small bowel, and most of colon is performed. Careful dissection is performed in the hilum of the liver. The liver needs to be preserved, and special attention to prevent injury to its structures is fundamental. Hepatic artery is identified and dissected down to the celiac trunk. Splenic artery will be tied. Gastroduodenal artery should be tied and divided. Main bile duct should be encircled and divided close to the pancreas. When all the organs are dissected and ready to be explanted, the stomach is transected; superior mesenteric artery is divided, and the portal vein should be divided as long as possible. The liver will remain perfused exclusively through the hepatic artery until the reperfusion of the new organs. Special and more laborious dissection occurs when patient presents with a hepatic artery from the superior mesenteric artery (Fig. 8).

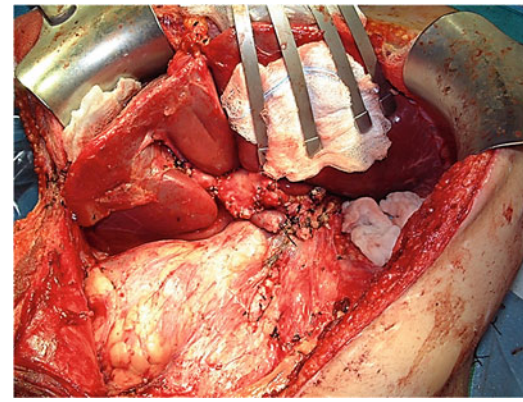

Fig. 8 Modified multivisceral recipient after the explant

Implant

Organs are brought to the field, and anastomosis of the portal vein is performed. End-to-end anastomosis is performed in a standard fashion with extra attention to avoid traction when the arterial reconstruction is done. Anastomosis of the aorta, stomach, pyloroplasty, and + – ostomy follows the same description as the multivisceral transplant. Reconstruction of the bile duct is performed in the standard way as done in a regular liver transplant. Roux-en-Y can be done as well.

Ostomy, No Ostomy, and Hybrid Ostomy

Historically, an ostomy was mandatory in intestinal transplant, and frequent endoscopies for mucosal evaluation were routine. For some patients, this is still the safest approach and commonly used among all transplant centers.

Biopsy and histologic evaluation is the gold standard for graft assessment in intestinal transplantation. Usually, a temporary ostomy is created to facilitate graft evaluation. Ostomy biopsies can be performed without sedation in most cases, and the risk of complication is minimal. However, ostomies are often associated with episodes of dehydration leading to readmissions, low patient satisfaction, and social limitations. In some patients, intestinal and multivisceral transplants can be selectively performed without an ostomy (Beduschi et al. 2015, #3). Nevertheless, patients need sedation for colonoscopies, a not well tolerated colon preparation, and the graft cannot be evaluated early in the postoperative period due to increased risk of perforation. Potential delays in the diagnosis of rejection may be another risk of not performing an ostomy. For all these reasons, the need for an ostomy is customized based on the age, anatomical and surgical features, type of graft, and overall immunological risk.

Multivisceral transplants have a lower chance of rejection, and it has become customary not to perform an ostomy for these recipients (Beduschi et al. 2015, #2). Ostomies are only performed in special situations for multiviscerals recipients. A pediatric recipient weighing less than 10 kg requires an ostomy because it is very difficult to reach the terminal ileum through a regular colonoscopy. Patients with motility disorders and abnormal anorectal manometry require an ostomy in order not to compromise the entire graft given potential obstruction at the anastomosis. Another situation where an ostomy may be used in the multivisceral transplants is patients with no rectum or very short stump where the distal reconstruction is high risk for leaks. In these cases a loop ileostomy will protect the anastomosis.

Isolated intestines and modified multiviscerals recipients have increased immunological risk and require frequent graft evaluation. An ileostomy or colostomy is performed in a loop fashion or using the "Chimney or Bishop-Koop" technique. Some patients require a definitive ostomy, usually colostomy.

Of late, the concept of hybrid ostomy has been developed (Beduschi et al. 2015, #3). This technique combines the benefits of easy graft evaluation via a regular ostomy without the hurdles of having one. The hybrid ostomy is disconnected from the GI tract, keeping the vascular pedicle intact. That way, the patient has an ostomy without stool output. This hybrid ostomy technique was first described using the transplanted colon. It is well-known that the terminal ileum is the first part of the graft to present any pathological finding. It is not uncommon to simultaneously have normal transplanted colon and rejection in the terminal ileum biopsy. To maximize the graft evaluation, the original hybrid ostomy technique using the transplanted colon was abandoned and redesigned utilizing the terminal ileum. After reperfusion, proximal and distal anastomoses are performed in the standard way. Terminal ileum is divided 15 cm from the ileocecal valve using GIA stapler. Another GIA stapler is fired 15 cm proximally from the initial division. The mesentery is divided up to the base making sure vascular supply is preserved. Excluded 15 cm of the ileum is moved medially, and a side-to-side anastomosis in two layers is performed in the standard way between the two sides of the ileum. Defect in the mesentery is closed to prevent internal hernias. Ostomy is brought out to the skin and matured in standard fashion (Fig. 9). Hybrid ostomy combines all the benefits of not having a real ostomy with the advantage of histological evaluation of the graft without the risks and preparation of a colonoscopy. It is technically easy; patient satisfaction is high, and episodes of dehydration are rare. Ostomy takedown does not affect the intestinal function, and hospitalization is not required. Hybrid ostomy has become a standard procedure in some centers.

Colon Transplant, Pull Through, and Use of the Entire Colon

Colon is normally transplanted in all types of intestinal grafts. In a survey during the Congress of the Intestinal Transplant Association in 2017, all the major transplant centers include the colon as part of the transplant. Colon inclusion translates to less diarrhea, less episodes of dehydration, and overall higher patient satisfaction and quality of life. Usually, in the donor operation, the colon is divided at the level of the splenic flexure, respecting the superior mesenteric irrigation.

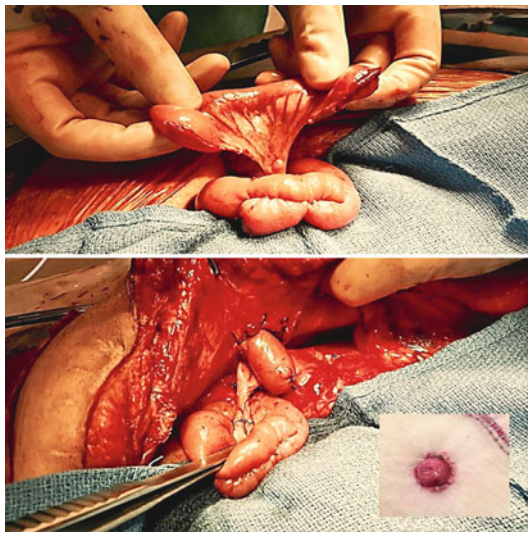

Fig. 9 Hybrid ostomy. Preserved vascular pedicle but not connected to the GI tract

In patients with motility disorders such as Hirschsprung's disease, or with previous resection of the rectum, the ability to restore the intestinal continuity is limited; hence, an end ostomy is the most common choice. A small intestinal pull-through is a common procedure used in pediatric surgery but very rarely used for transplant patients. More recently, pull-through operations to reconstruct this population using the transplanted colon have been performed (Beduschi et al. 2017) (Fig. 10). The reconstruction can be performed days after the transplant or even after years. A loop ileostomy is done to protect the colon-anal anastomosis and early graft surveillance.

Sometimes the colonic graft may not be long enough to reach the pelvis when it's divided at the splenic flexure. In that case, transplant of the entire colon, including descending and sigmoid,

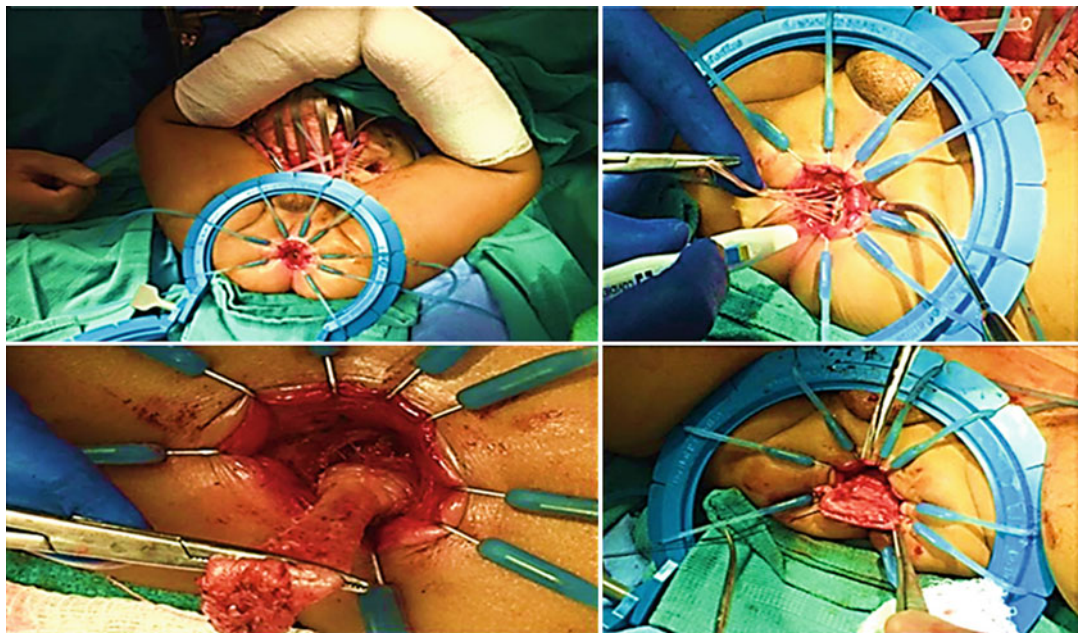

Fig. 10 Pull-through operation 3 days after a multivisceral transplant in a pediatric patient with Hirschsprung's disease

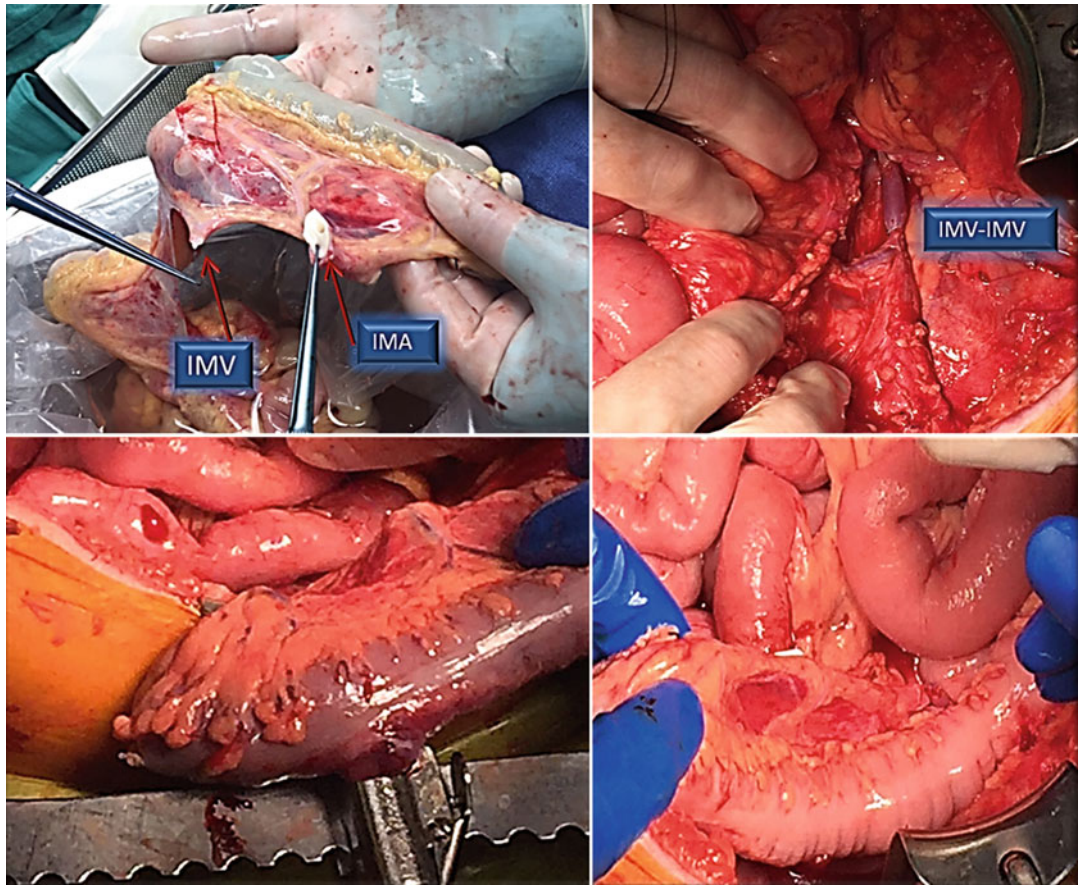

Fig. 11 Transplant of the entire colon. On the bottom, after the reperfusion of the main graft and then after the reperfusion of the inferior mesenteric vessels. Note how the sigmoid becomes pink

is possible. For multivisceral grafts, it is important to preserve the inferior mesenteric vein, and only the reconstruction of the inferior mesenteric artery may be needed. In case of the isolated intestinal/colon grafts, the reconstruction of inferior mesenteric vein and artery is necessary. Reconstruction may be performed orthotopically in the inferior mesenteric vessels or heterotopically in the vena cava and aorta (Beduschi et al. 2017) (Fig. 11).

An important technical detail about colon transplant is the middle colic vein. It is not a problem for the multivisceral grafts, because the organs are "en bloc" and torsion of the superior mesenteric vein does not happen. However, it is critical for the isolated intestine (intestine-colon) grafts. After reperfusion and when the distal reconstruction will be performed, extra care should be taken to avoid torsion of the colic vein when rotating the colon. It can happen more commonly with systemic drainage than with portal drainage. After colonic reconstruction is performed, it is important to check the orientation of the superior mesenteric vein and look for signs of graft venous congestion. Torsion of the vein is a catasthrophic complication leading to graft loss if not immediatelly identified.

Colonic anastomosis can be performed in different ways: side to side, end to side, and end to end, usually in two layers hand sewing and without the use of stapler devices. It is important to keep in mind, mainly for the patients without an ostomy, the angle and position of the colon that will facilitate a colonoscopy in the future, making access to the terminal ileum easier.

Closure

Abdominal cavity, or lack thereof, is a common problem in intestinal transplantation. Patients lose the abdominal domain due to multiple resections. It is often difficult to find organs that will fit without closure problems. Multiple techniques have been described to achieve complete closure of the abdomen after transplant (Mangus et al. 2012). The use of biological mesh (*alloderm*) is preferred to close the fascia in the majority of patients when primary closure is not possible (Selvaggi et al. 2009). It is easy to manipulate, and it does not have to be removed in the presence of infection (Fig. 12). In extreme and rare cases, abdominal wall transplant can be performed (Gondolesi et al. 2009) (Fig. 13).

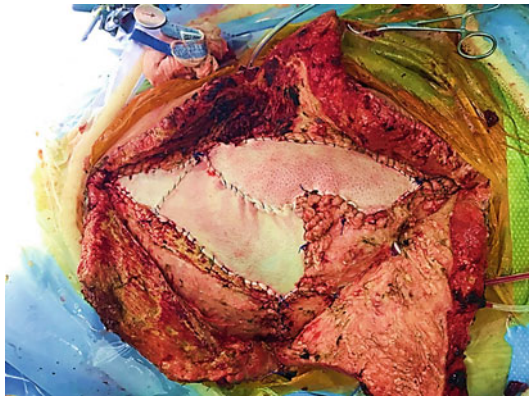

Fig. 12 Huge abdominal defect closed with alloderm mesh. Skin is closed after raising skin flaps

Conclusion

Visceral transplantation is still a rare and very specialized procedure. Recent advances in patient and graft survival, in part, are due to the refinement of the surgical techniques described here. Surgical complications still exist, but they are no longer the Achilles heels of these operations. This chapter describes a combination of classic and

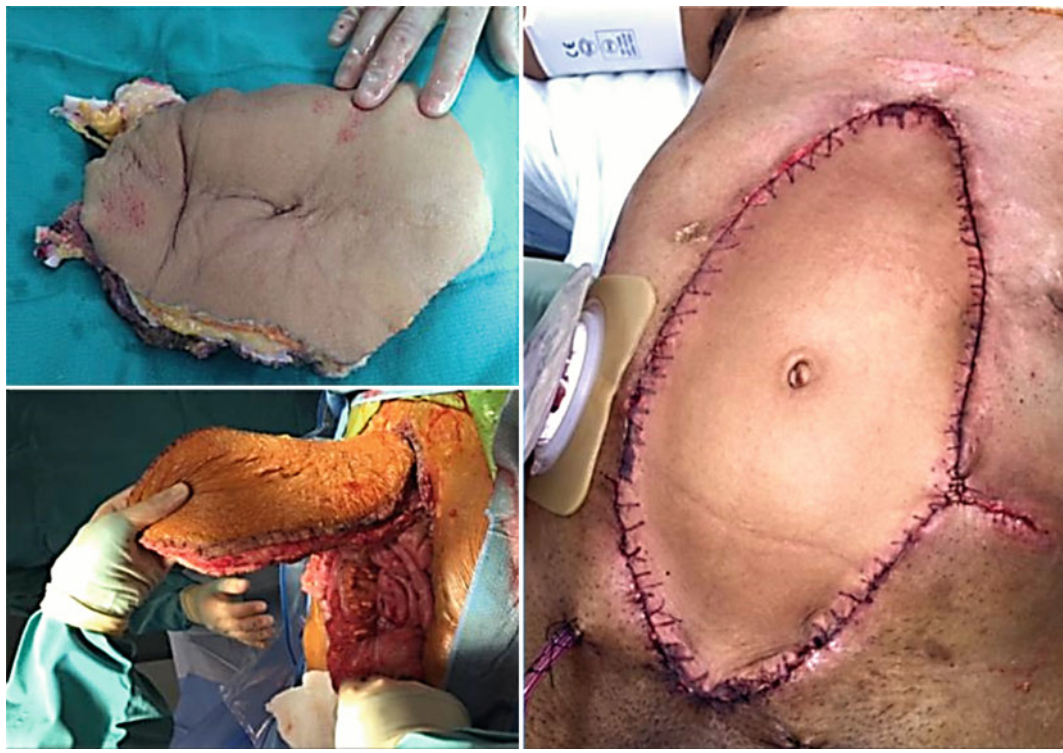

Fig. 13 Abdominal wall transplant combined with intestine-colon transplant

newer techniques and reflects solutions and evolvement based on hundreds of cases over more than 10 years.

Cross-References

► Donor Selection and Operation

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Donor Selection and Operation

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Abstract

Over recent years, small intestine transplant is considered to be an effective treatment option for intestinal failure. Donor selection and donor operation are important to successful transplantation. Efforts have been focused on developing ways to safely increase the donor pool. For example, improvements in the detection of infection and malignancy in donors have facilitated increased graft utilization in high-risk populations. Additionally, operative techniques have been established to allow transplant of multiple abdominal organs en bloc (multivisceral and modified multivisceral transplant), as well as for intestine transplant alone, increasing organ yield from individual donors. Despite this trend toward inclusivity in intestine transplant, the operation remains to be associated with inherent risks, due to the immunologic complications. Therefore numerous factors, including age, medical history, graft function, and hemodynamic stability, remain vitally important when selecting a suitable donor organ.

Keywords

Intestine transplant · Multivisceral transplant · Modified multivisceral transplant · Donor selection · Procurement operation

Introduction

Improvement in short-term outcomes following intestine transplantation has led to an increase in demand for this organ. The active wait list for intestinal transplants in United States has increased from 71 at the end of 1999 to 270 in 2017 (Smith et al. 2018). At the same time, the United States has seen significant improvement in both time to transplant and wait list mortality; median time to transplant is 265 days, and the wait list mortality has decreased from 50% (1999) to 21% (2016). Despite this fact, the wait list mortality for patients awaiting intestinal transplant remains significantly higher than that of other abdominal solid organs (Smith 2018; Kim et al. 2018; Hart et al. 2018). Currently, intestinal grafts are recovered from approximately 1% of total deceased donor pool. While these figures may argue for increased utilization of donor intestines, intestinal transplant remains a highly invasive operation with major risks, including infection, thrombosis, and bowel necrosis. Thus, careful donor selection and proper organ procurement remain vital components of successful transplantation.

Allocation Policy and Utilization

Although selection of donors is largely based upon age, habitus, and hemodynamic status at time of death, allocation policies greatly influence how procured organs are utilized. Intestine only transplants are distributed in a fairly straightforward fashion, with organ allocation primarily determined by ABO compatibility and regional proximity. Additionally, patients can receive a designation of *Status 1* for specific medical indications necessitating urgent transplantation. These include abnormalities in liver function tests or loss of vascular access for total parenteral nutrition, both in the setting of intestinal failure. *Status 1* patients receive priority for intestine transplant within a given region (Organ Procurement and Transplantation Network 2018).

Patients with intestinal failure can have coexisting liver disease (from primary disease processes or complications stemming from long-term TPN), often necessitating simultaneous liver-intestine transplant. Under these circumstances, patients are listed on both the intestine and liver waiting lists. Their status on the liver list alone, however, is what determines their organ allocation. Priority on the liver wait list is dependent on the MELD/

PELD score, which is used as a metric for the severity of a patient's liver disease. This score ranges between 6 and 40, with a higher score indicating more severe liver disease and a more immediate need for transplant. Although liver-intestine transplant candidates have very high pretransplant mortality, their liver disease is often not severe enough to warrant transplant based on their natural MELD/PELD score alone. To avoid excessive wait list mortality, patients listed for combined liver and intestine transplant are given a MELD/PELD exception score of 29. This provides liver-intestine recipients priority over patients listed for liver transplant alone with a lower MELD/PELD score. Should a liver-intestine transplant candidate's liver function deteriorate while awaiting transplant such that their natural MELD/PELD is greater than their original exception score, they will be listed at the higher of the two scores (Organ Procurement and Transplantation Network 2018).

Donor Selection Criteria

Overview

Broadly, heart-beating cadaver donors appropriate for transplantation of other abdominal organs and without any gastrointestinal disease are considered suitable for intestinal donation. Ideally, a deceased donor for intestinal transplant is a young, ABO compatible donor, who has remained hemodynamically stable until time of procurement, has no underlying infectious or malignant processes, and has normal liver and kidney function.

Currently, approximately 35% of total donors meet these criteria. Unfortunately, in the United States, a significant percentage of potential intestinal grafts are not utilized – a study from 2012 determined the number of grafts recovered to be between 0.0 and 0.8 per eligible donor. The overall rate of intestines recovered for transplant and not transplanted was 8% in 2016 (Organ Procurement and Transplantation Network 2018). This suggests that underutilization of intestinal grafts may be a greater contributor to wait list times than organ availability.

To combat this effect, some centers have broadened their inclusion criteria for donor organs. A 2008 study showed 15% of the transplanted intestines failed to meet at least one of the criteria mentioned above – the most common being elevated serum creatinine, cardiac arrest >15 min, or the use of more than two ionotropic agents at the time of procurement. The use of donations after circulatory death (DCD) has also been considered to increase the size of the donor pool. Although large-scale outcome data specific to DCD intestine transplant is not available, similar studies have been performed comparing DCD and donation after brain death (DBD) liver transplants. While these show comparable 5-year survival rates for graft and patient, they also demonstrate an increase in ischemic organ injury (measured by AST and ALT peaks at 24 h) and increased incidence of structural organ damage (nonanastomotic biliary strictures) in the DCD patient arm (Meurisse et al. 2012).

Intestine is considered to be more sensitive to ischemia than other solid abdominal organs, as ischemia/reperfusion injury is associated with allograft dysfunction, impaired mucosal defense, and enhanced bacterial translocation. Although these principals are based largely on anecdotal evidence, the risks are great enough that intestinal transplantation remains largely restricted to optimal donors.

Donor Age

Considering that there are comparatively fewer patients waiting for intestinal transplantation, matching recipient and donor age is not required. Younger donors are preferred, with donors <50 years of age being considered as optimal for intestinal or multivisceral transplantation (MVT). Of a total of 2673 total intestinal transplants performed in the United States, 99.5% were from donors <50 years old. Donors less than 18 years composed more than two-thirds of the total donor pool, and one-fourth of those were infants. These trends have remained true in recent years. According to the 2016 OPTN/SRTR Data Report, the largest proportion of donors were aged 18–34 years (34.8%), followed by those aged

younger than 5 years (32.9%). Less than 10% of donors were over the age of 35 years (Organ Procurement and Transplantation Network 2018).

Donor Size and BMI

Both donor size and BMI must be considered in the procurement process for several reasons. First, patients requiring intestinal transplants have frequently lost their abdominal domain due to repeated abdominal procedures, loss of small bowel, or growth retardation. To allow for tension-free abdominal wall closure after transplant, donors with weight ranging from 50% to 80% of the recipients are sought after. In the event that, after weight matching, a donor graft remains too large for the recipient, graft resection is appropriate (Bueno et al. 2000; Reyes et al. 1998).

Donors with body mass index <30 lb./m2 are usually considered suitable for intestinal or multivisceral transplantation. This is to avoid posttransplant complications that may arise from fat deposition within graft organs, particularly in the setting of MVT. For example, an MVT from an obese donor may contain a significant amount of fat within the pancreas. This has been documented to contribute to posttransplantation pancreatitis upon reperfusion – a catastrophic complication that may require re-transplantation. Hepatic steatosis may be present in grafts from obese donors, which has been associated with hemodynamic instability after reperfusion. Additional studies have demonstrated that steatotic livers are associated with reduced graft function and decreased graft survival (Chu et al. 2015).

Infection and Malignancy

Donors may have had exposures to infections and may carry transmittable disease. Of particular concern in the setting of intestine transplant are infections by HIV, HBV, and HCV. To delineate potential carriers, the CDC has defined criteria for adult high-risk donors (HRDs). These include individuals who have a history of incarceration, IV drug use, repeated transfusions of blood products for clotting disorders, or sexual contact with other high-risk individuals (Humar et al. 2010). According to CDC guidelines, organs from HRDs should not be transplanted unless the risks associated with viral infection are outweighed by the potential benefits of transplantation in the patient (Provisional 1985; Rogers 1994). Should circumstances be such that grafts from a HRD are to be used, nucleic acid amplification testing (NAT) should be considered to reduce risk of infectious disease transmission. NAT is particularly useful in screening for HIV, HBV, and HCV infection, as it can detect viral infections during window periods and earlier in their course of infection than conventional serologic methods allow (Humar et al. 2010).

Although NAT has demonstrated effectiveness in reducing inadvertent viral transmission and has increased rates of organ utilization from HRDs, there is insufficient evidence to recommend universal prospective screening of all organ donors for HIV, HBV, and HCV (Humar et al. 2010). Current concerns are that the false-positive rate associated with NAT, particularly in average-risk donors, may result in overall loss of donor organs should universal testing be implemented (Zou et al. 2004). Additionally, NAT may cause delay in organ procurement or increase cold ischemic time, resulting in reduced utilization and poorer graft outcomes (Hwang et al. 2005; Segev et al. 2008).

Risk of transmission of malignancy from donor in the setting of intestinal transplantation is rare due to relatively younger age of the donors. However, as patients face chronic immunosuppression posttransplant, the risk must not be overlooked. Overall donor-derived malignancy is found in about 0.02–0.4% of solid organ recipients (Morath et al. 2005; Green et al. 2015). Due to lack of organized approach to assess the risk of donor tumor transmission, an ad hoc Disease Transmission Advisory Committee (DTAC) of the Organ Procurement and Transplantation Network/United Network for Organ Sharing (OPTN/UNOS) was formed to advise on this subject. The committee recommends the use of organs from donors with minimal risk (<0.1%) of tumor transmission with clinical judgment and an informed

consent from the recipient. In organ recipients at high risk of mortality without transplant, the use of organs from donors with low risk ($0.1\% < x < 1\%$) of tumor transmission is appropriate. The risk stratification of various malignancies is described elsewhere and is beyond the scope of this chapter (Nalesnik et al. 2011).

Donor Physiology

ABO Typing

ABO compatible organs are typically used for intestinal/multivisceral transplantation. Blood type O donors can be used for recipients with blood types A, B, and AB. There have been case reports of severe hemolysis following ABO-mismatched intestinal transplant (Davis et al. 2011).

Hemodynamic Status

To optimize immediate allograft function, donor selection has historically been restricted to donors with hemodynamic stability, normal arterial oxygenation/perfusion, and minimal inotropic/vasopressor support. The requirement of cardiopulmonary resuscitation in a donor, prior to graft procurement (downtime), is not a considered to be a direct contraindication for intestinal donation (Matsumoto et al. 2008). Minimal downtime, however, is preferable. Likewise, donors requiring little to no vasopressor support are ideal for graft donation – in vitro studies have demonstrated reduced SMA blood flow and thus intestinal perfusion, when vasopressin was required for hemodynamic support in brain death models (Martikainen et al. 2010).

Gastrointestinal Function

As with any other transplantable organ, it is important to ensure adequate intestinal graft function prior to procurement. A detailed medical history of the donor should be obtained when possible, with previous history of gastrointestinal disease ruling out donors from intestinal donation. A history of events leading to hypoperfusion, such as trauma, MI, or sepsis, should be elicited, as these episodes may contribute to "shock bowel" in potential donors. Elevated arterial lactate levels may be used as an indicator of bowel ischemia in the setting of recent hypotension. Donors should also be assessed for history of blood in stools, chronic diarrhea, persistent vomiting, or requirement of enteral feedings. There is concern that long-term antidiarrheal therapy can contribute to bowel atony, so a good medication history should be obtained as well (Saunders and Kimmey 2005).

Liver and Pancreas Function

In the case of a multivisceral or liver-intestine transplantation, it is important to evaluate the condition of extraintestinal organs. Elevated transaminases (AST/ALT) may indicate hepatocellular necrosis, while elevations in amylase/lipase may indicate pancreatitis following cardiopulmonary arrest/resuscitation. Such grafts are usually not considered for multivisceral transplantation. However, if grafts demonstrate improving liver function tests and appear normal on biopsy during the time proceeding transplant, they may be reconsidered. Additionally, it is imperative to rule out undiagnosed diabetes in the donor, via HbA1c, as its presence is concerning for endocrine pancreatic insufficiency posttransplant.

Donor Operation

Donor Preparation

A thorough examination of the donor is performed prior to beginning the procurement operation. As many grafts become available as the result of trauma, it is important to note evidence of physical insult that may compromise the integrity of internal organs. Radiologic studies, when available, are invaluable in this setting. CT can be used to assess for shock bowel, perforated viscus, or damage to solid organs. Contrasted studies can illuminate vascular abnormalities that may be present. Although this information may help the surgeon to assess the feasibility of an operation, procurement should not be delayed for such studies to be performed.

Once in the operating room, a nasogastric (NG) tube is placed in the donor. Prophylactic

antibiotics are administered parentally at this time. Significant translocation of enteric flora has been reported following intestine transplant, which is thought to contribute to postoperative infection rates (Cucchetti et al. 2009). Thus, some centers administer antibiotic and antifungal agents via NG tube at this point, with the goal of decontaminating the donor gut. Recent studies, however, have shown there to be similar rates of postoperative infection in a population of intestine transplant patients whose grafts were not decontaminated prior to procurement (Clause et al. 2018). Therefore, selective gut decontamination may be unnecessary in the setting of small intestine transplant.

The donor is prepped for the operation from neck to mid-thigh, as it may be necessary to procure vessels of these regions for vascular reconstruction in the graft. A midline thoracoabdominal incision is made, along with a median sternotomy. Additionally, cruciate extensions, along the bilateral abdominal walls, are made from the midline incision to enhance operative exposure.

Phases of Operation

The procurement operations for multivisceral, modified multivisceral, and intestine only grafts are each performed in three basic phases. First is the warm dissection phase, during which the donor's circulation remains intact. During this portion of the operation, the surgeons gain access to the peritoneal cavity and inspect the viscera for evidence of trauma, ischemia, or other gross abnormality. The liver is examined for steatosis and its vascular supply is determined. The lesser sac is opened, allowing for visualization and palpation of the pancreas. The surgeons then begin to dissect relevant anatomical structures.

Upon completion of the initial dissection, the cold dissection phase of the operation begins. The donor abdominal aorta is cannulated, and cold preservative solution is infused. Simultaneously, the inferior vena cava is sharply transected above the level of the diaphragm, permitting exsanguination of the donor. Commonly used preservative solutions during intestinal/multivisceral procurements are histidine-tryptophan-ketoglutarate (HTK) and University of Wisconsin (UW) solutions. Multivisceral/intestinal grafts preserved in UW and HTK demonstrate no difference in graft and patient survival posttransplant. Studies show no differences in initial function or endoscopic appearance of graft organs, rejection episodes, or incidence of transplant pancreatitis (Mangus et al. 2008). The donor's abdominal cavity is packed with ice, and, following an adequate cooling period, the graft is completely dissected and removed from the field.

Following transport to the recipient institution, the graft is prepared for implantation during the third phase of the operation. This process is known as back table preparation. The graft is further inspected and dissected. Vascular reconstruction is performed to facilitate efficient implantation, given the recipient's anatomy. It is at this point that the donor operation is considered complete.

Organ Procurement

Multivisceral (En Bloc Liver, Stomach, Pancreas, and Small Intestine) Procurement

After access to the peritoneal cavity has been obtained, and adequate organ inspection has occurred, the liver is mobilized through takedown of the triangular ligaments with electrocautery. The greater omentum is then divided from the stomach along the greater curvature, with care taken to preserve the gastroepiploic arcade. The small intestine is wrapped in a wet laparotomy sponge and retracted cephalad. Ascending colon is then mobilized after dividing the lateral peritoneal reflection along the white line of Toldt. The ascending colon is then divided with a GIA linear stapler about 6 inches from the ileocecal valve. Dissection is carried along the entire colon, with division of gastrocolic and lineo-colic ligaments. After ligation and division of the middle colic, left colic, and inferior mesenteric vessels, a colectomy can be completed. The middle colic vessels can be preserved at this stage should it be necessary to transplant more than just the cecum. The small intestine is now free from its attachment with the large bowel.

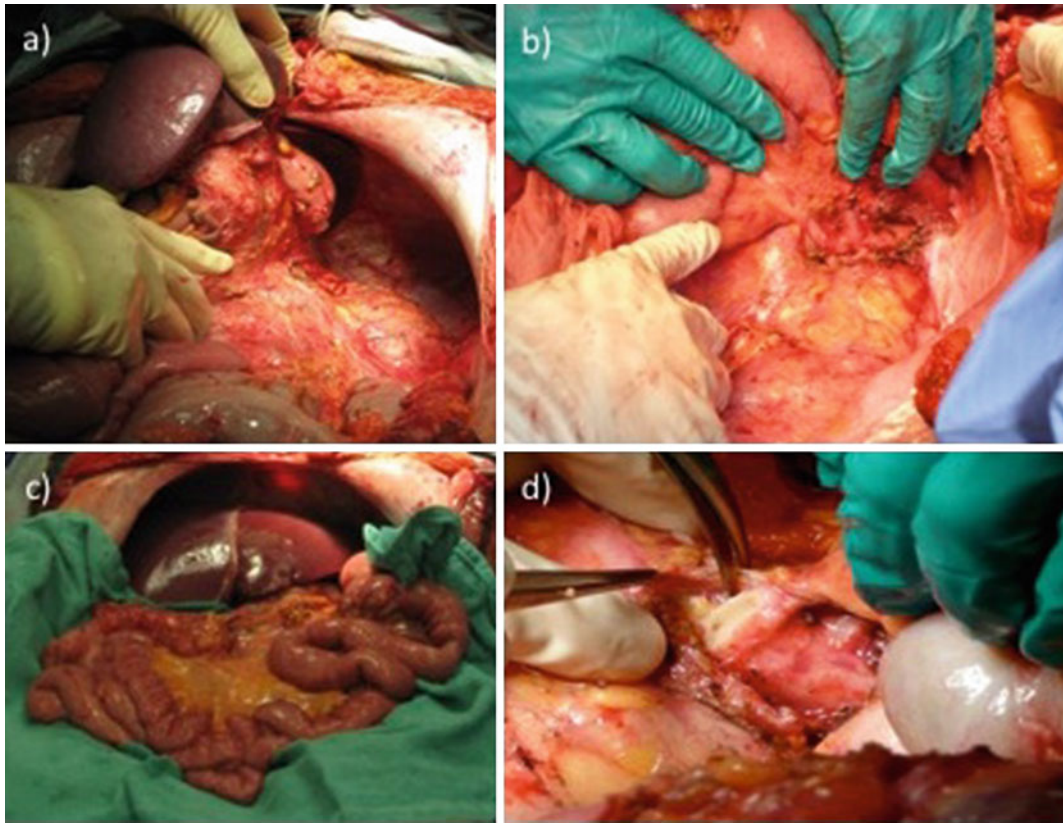

Fig. 1 Multivisceral (en bloc liver, stomach, pancreas, and small intestine) procurement. (**a**) The spleen can be used as a handle for mobilization of the pancreas from retroperitoneal structures after dissection of the spleno-phrenic ligament. (**b**) Visualization of the SMA and celiac axis after dissection of the celiac ganglia. (**c**) Ideal graft orientation prior to cold perfusion flush – proper anatomic position optimizes the flushing of blood from graft vasculature. (**d**) The abdominal aorta should be sharply transected between the origin of the SMA and the renal arteries

In the next phase of the operation, the duodenum is reflected using a Kocher maneuver to expose the suprarenal vena cava. The posterior peritoneal reflection of the root of mesentery is then divided to expose the infrarenal aorta, vena cava, and the left renal vein. The inferior mesenteric vein is ligated and transected. Dissection is continued along the inferior border of the pancreas, dividing within the avascular peritoneal reflection. The spleen is then mobilized by dividing the spleno-phrenic ligament; the spleen can now be used as a handle to mobilize the entire pancreas from the retroperitoneal structures (Fig. 1a). At this point, the peritoneal reflection along the fundus of the stomach and esophagus should also be divided.

Now, the superior mesenteric artery (SMA) can be identified just above the left renal vein. The celiac ganglion is divided to further visualize the SMA and the celiac axis (Fig. 1b), with care taken to preserve as much ganglionic tissue with the graft as possible. The infrarenal aorta is then encircled for eventual cannulation. The gallbladder is opened using electrocautery and the bile is flushed out. The cystic duct is left intact. As this is an en bloc procurement, the hepatic pedicle is not dissected. The supraceliac aorta is then identified after dividing the overlying diaphragmatic crus – this will be the location of proximal cross clamping during cold perfusion stage.

Prior to initiating the cold perfusion flush, the patient is heparinized with 100 IU/kg of heparin.

The infrarenal aorta is cannulated, and then the graft is placed in its anatomic position, with the mesentery as flat as possible, to optimize the flushing of blood from the graft vasculature (Fig. 1c). A non-traumatic vascular clamp is the applied on the supraceliac aorta, well away from the takeoff of the celiac trunk, and the graft is flushed with cold preservative solution. Inferior vena cava is cut flush to the diaphragm in the pericardial cavity to allow for venous runoff. Ice-slush is placed on the organs, and the effluent from the suprahepatic vena cava is monitored periodically for presence of blood. It is recommended to flush the graft with 3–4 L of histidine-tryptophan-ketoglutarate (HTK) or University of Wisconsin solution in adult donors (Mangus et al. 2008). For pediatric donors, approximately 100–200 ml/Kg of the perfusion solution is used.

After having flushed the graft, the cold dissection phase (post-exsanguination) begins. The liver is first mobilized by sharply cutting the diaphragm. The inferior vena cava is then transected proximal to the renal veins. The abdominal aorta is sharply divided between the takeoff of the SMA and the renal arteries (Fig. 1d). An attempt is made to preserve an aortic cuff of the SMA, although the SMA originates at the level of the renal arteries in younger donors, which can prevent the procurement of an aortic cuff for either vessel. Cranially, the aorta is transected distal to the origin of the left subclavian artery. The entire abdominal and descending thoracic aorta is then freed from the spine by dividing the intercostal arteries (Abu-Elmagd et al. 2000).

The nasogastric tube is removed, and the esophagus is stapled well away from the gastroesophageal junction. The en bloc graft is now free from any remaining abdominal attachments, completing the cold phase of the procurement. The organs are removed from the abdominal cavity and stored in cold preservation fluid for transport to recipient location.

Modified Multivisceral (En Bloc, Stomach, Pancreas, and Small Intestine) Procurement

A modified multivisceral (MMV) graft consists of a donor stomach, pancreaticoduodenal complex, and small intestine. Thus, the procurement is essentially similar to the en bloc multivisceral procurement, described above, except that the donor liver must be separated from the rest of the graft. This usually takes place in situ, during the cold (post-exsanguination) phase of the procurement. To reduce cold ischemic time, however, it is important to perform meticulous dissection of the hepatic pedicle during the warm phase of the operation. This is accomplished by ligating the common bile duct near the duodenum and dividing proximally. The proper hepatic artery is then identified and dissected to identify the origin of the splenic artery. Following initiation of the cold phase of dissection, the liver is separated from the rest of the graft. To do so, the portal vein is divided proximal to the coronary vein, and the proper hepatic artery is divided a few millimeters distal to the origin of the splenic artery. If the liver and MMV graft are being transplanted at the same center, the whole graft can be procured as a multivisceral graft and then be separated at the recipient hospital. However, it is preferred to separate the liver in situ, during the cold phase of the procurement. The remaining part of the cold phase is similar to that of the multivisceral procurement. The donor liver can then be transplanted separately from the rest of the MMV graft.

For MMV transplantation, the left gastric and splenic arteries are preserved with the graft, maintaining arterial supply to the stomach and pancreas. As described above, this requires division of the hepatic artery distal to the origin of the splenic artery, retaining a stump of the hepatic artery proper for the implantation of the recipient's liver. At the beginning of the procurement, it is important to look for accessory/replaced hepatic arteries, arising from the SMA (right-replaced) or left gastric artery (left-replaced). In the presence of a left accessory hepatic artery, MMV procurement is difficult, as the left gastric artery usually must be sacrificed to the liver graft along with the accessory hepatic artery. However, when the left accessory hepatic artery is of adequate size, the gastroduodenal artery can be used to reconstruct the left hepatic artery (Fig. 2). This technique allows for the surgeon to retain the left

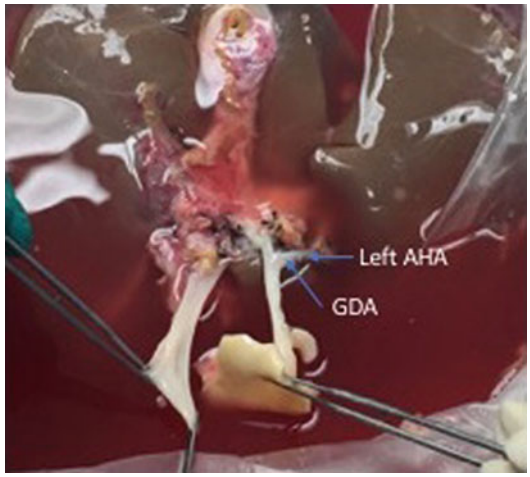

Fig. 2 Reconstruction of left accessory hepatic artery using donor gastroduodenal artery. This technique preserves arterial supply to the liver while allowing the left gastric artery to remain with the MMV graft

gastric artery with the MMV graft, permitting separate liver and MMV transplantation (Fridell et al. 2009).

Should a right accessory hepatic artery be present, this vessel can be divided away from its origin off the SMA and reconstructed with the gastroduodenal artery in a similar manner as described above (Fridell et al. 2009). In smaller donors, such as pediatric populations, vasculature is smaller. As such, the SMA may be procured with the accessory right hepatic artery to allow for successful liver transplant. In those cases, priority is given to the liver transplant, and MMV procurement is not pursued. The indications for MMV transplant, however, are rare in pediatric patients, and this procurement is usually not performed in pediatric donors.

When the proper hepatic artery is relatively small in caliber, the liver transplant surgeon may wish to have the entire celiac axis to perform a relatively wider anastomosis using a Carrel patch. To overcome this issue, a vascular reconstruction technique has been described (Fridell et al. 2009). In this technique, the hepatic artery is not transected distal to the splenic artery. Instead, the splenic artery is transected as if the pancreas were being procured for isolated pancreas transplantation. The celiac axis is then transected between the origins of the hepatic and left gastric arteries, leaving enough of a vascular cuff to allow an anastomosis without compromising the lumen of the hepatic artery. On the back table, the distal celiac axis beyond the origin of the left gastric artery is then anastomosed end-to-end to the splenic artery using 7–0 prolene suture.

Isolated Small Intestinal Procurement

The procurement of isolated small intestinal grafts shares the initial warm dissection steps of a complete multivisceral procurement, including colectomy. At this point, the root of the small intestinal mesentery is dissected in order to isolate the superior mesenteric vessels. The small intestine is wrapped in a wet laparotomy sponge and gently retracted caudally, revealing the peritoneal fold over the front of the mesenteric root. This is opened to expose the superior mesenteric vein (SMV) laterally and the SMA medially (Fig. 3). The middle colic artery, previously ligated for colectomy, can also be followed proximally to identify the SMA. By dividing small venous tributaries and arterial branches, short segments of the main trunks of both the SMA and the SMV are prepared for division in the cold phase through division of their small arterial and venous branches. The SMV is usually dissected distally to the point where there is only a single branch. Dissection of the SMA should be limited proximally to the origin of middle colic artery to avoid damage to the inferior pancreaticoduodenal artery. Exposure of the posterior wall of the SMV and SMA is optional and is preferably done in the cold phase of the procurement. The proximal jejunum is divided using a GIA stapler after dividing the ligament of Treitz and the inferior mesenteric vein. The mesentery of the proximal jejunum is then divided by ligating jejunal vessels. The jejunum should be examined for any signs of ischemia following ligation of its arterial branches; any ischemic segments should be resected at this time. The goal of this mesenteric dissection is to procure small intestine supplied by a single artery and vein, which will allow for easy anastomosis in the graft recipient (Fig. 4).

The procurement of an isolated intestinal graft becomes technically demanding when pancreas is

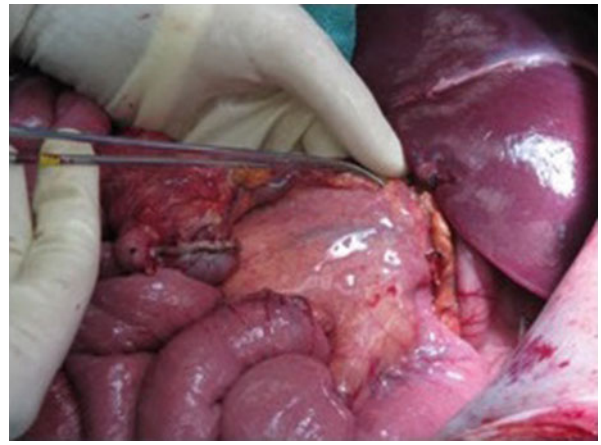

Fig. 3 Peritoneal fold overlying the mesenteric root. This can be opened to gain access to the SMA and SMV during isolated small intestine procurement. The SMA can also be identified by following the middle colic artery, previously dissected during colectomy

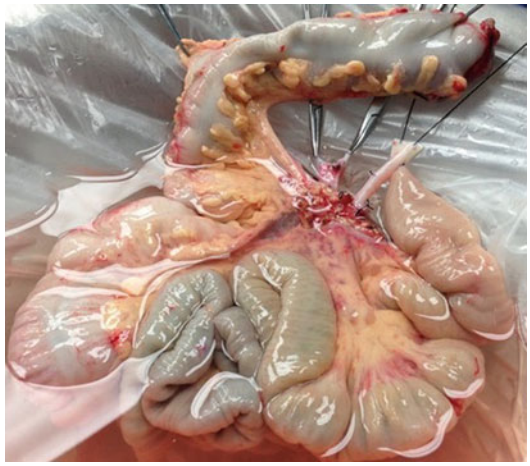

Fig. 4 Successful mesenteric dissection during isolated small intestine procurement yields a graft with a single arterial and venous supply. This facilitates easy anastomosis with the recipient's vasculature during implantation

being procured simultaneously. There is a significant variation of the anatomy of proximal jejunal branches, and it is not uncommon for a major jejunal branch to originate from the SMA proximal to the origin of the middle colic artery. In this case, the jejunal branch will not be included in the intestinal graft, requiring sacrifice of a portion of proximal jejunum. It is for this reason that the dissection of the mesentery is performed in the warm phase of the procurement, as devascularized jejunum can be identified following vessel ligation.

During the cold phase of the procurement, the intestinal graft is placed in anatomical position, with the mesentery flat, with care taken to ensure that the whole graft is not twisted across its vascular pedicle. The graft is flushed with cold perfusion solution as described above. After cross clamping and flushing of the graft, the superior mesenteric vessels are divided sharply. If the pancreas is being procured simultaneously, the pancreatic ends of the SMA and the SMV are tagged with a suture to prevent retraction of vasculature into the graft. If the posterior wall of the SMA and SMV was not exposed during the warm phase, this dissection is now performed. The intestinal graft can then be removed from the field and stored in cold perfusion solution.

Procurement of Additional Vasculature

Additional vessels are required to fashion the vascular anastomoses during implantation. The useful vessels in are iliac vessels with its branches, the thoracic aorta, and carotid arteries particularly the brachiocephalic artery with its bifurcation. Traction injuries to the vessels should be avoided to prevent intimal tears, which may result in arterial thrombosis.

Back Table Preparation

Preimplantation preparation of a multivisceral/intestinal graft is an important phase of the transplant operation. It provides an opportunity to carefully inspect the graft for any gross abnormalities,

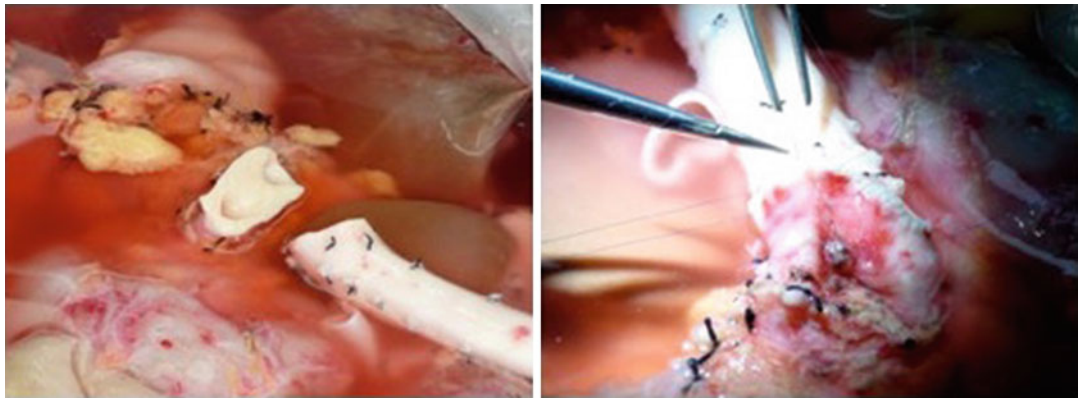

Fig. 5 (**a**) Multivisceral graft with single aortic patch, containing the origins of the SMA and celiac axis. (**b**) This is anastomosed end-to-end with a graft of donor thoracic aorta to establish a single anastomotic site

which may prevent a substandard organ from being transplanted. Detailed dissection of the graft is performed, and sites of vascular anastomosis are identified for further exposure. Vascular reconstruction is performed to better tailor the graft to the specific anatomy of the recipient. Meticulous backbench preparation produces optimal conditions for implantation, serving to reduce warm ischemia time and post-reperfusion bleeding.

The backbench preparation of a multivisceral graft includes splenectomy, esophagectomy, preparation of the vena cava, and preparation of the arterial inflow. There are two options for creating arterial inflow, with either a thoracic aortic conduit or the iliac bifurcation, each procured from the donor, being suitable for this purpose.

Thoracic aorta is prepared by ligating all the intercostal arteries flush to the aorta. The aorta is then tested for any leaks. As the multivisceral graft has the origins of the SMA and the celiac axis on a single aortic patch (Fig. 5), this patch is sewn to the thoracic aorta in an end-to-end fashion, usually with a 6–0 prolene suture, to complete the vascular reconstruction. Alternatively, the common iliac artery and its bifurcation can be used. In this technique the celiac artery and the SMA are separated and then anastomosed to the internal iliac artery and to the external iliac artery, respectively, also in an end-to-end fashion using 6–0 or 7–0 prolene suture (Fig. 6). These techniques successfully place the origins of the celiac artery and the SMA on a single vessel, so that only one arterial anastomosis to the recipient aorta is required for revascularization of the graft.

The backbench preparation of a MMV graft is similar to that of multivisceral; however there is no donor vena cava to prepare. The outflow of this graft is via the portal vein, which is trimmed to an appropriate length for anastomosis on the back table. The backbench preparation of an isolated intestinal graft is even more minimal. Typically, if a pancreas allograft has been procured simultaneously, the SMA and the SMV may need extension grafts sewn. However, when isolated intestinal graft is being sewn to the recipient SMA and SMV, extensions are usually not required. Should vascular extensions be needed, the external iliac artery usually matches the lumen on the SMA and is used for the arterial extension. Likewise, the external iliac vein is used for the SMV. If the liver and pancreas are being transplanted as well, the iliac vessels will be sacrificed to these grafts. The internal carotid artery can be used for the arterial extension under these circumstances.

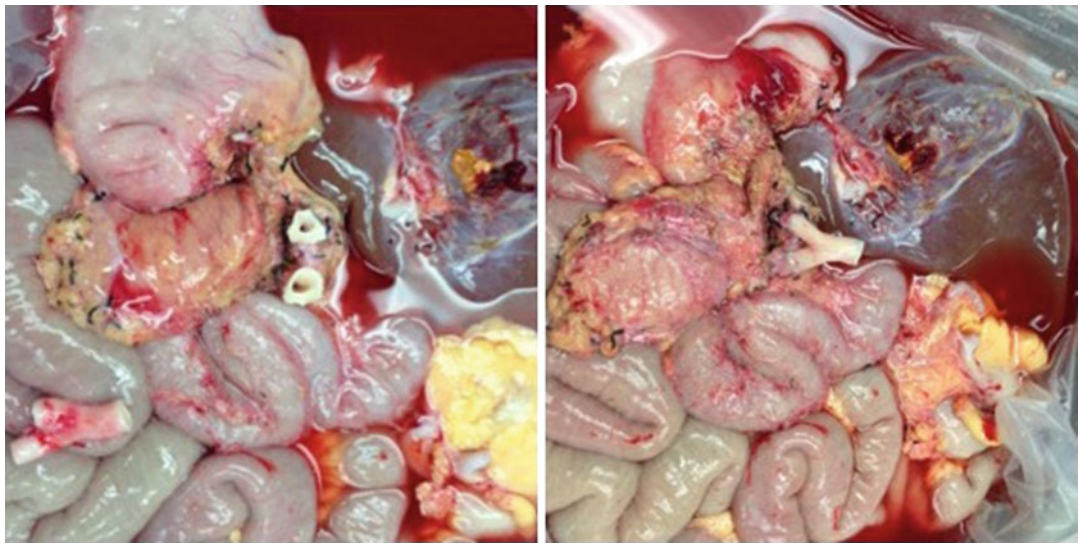

Fig. 6 (**a**) The origins of the celiac axis and SMA are sometimes separated from their shared aortic patch. (**b**) The bifurcation of the donor's common iliac artery can be used to fashion a single arterial anastomotic site. The celiac origin is sutured end-to-end with the internal iliac, while the origin of the SMA is anastomosed to the external iliac branch

Conclusion

Proper donor selection and graft procurement remain an important factor in producing successful multivisceral/intestine transplant outcomes. Thus, while there exist efforts to improve overall graft utilization, these must be balanced against the potential risks that may be introduced to recipients. Continued work in operative technique will be important to ensure that technically demanding graft procurement from otherwise suitable donors is not a barrier to successful transplantation. Another potential source for intestinal grafts may be in living donor transplantation. This area, however, requires further study regarding morbidity and mortality for both donor and recipient.

Cross-References

- ▶ Live Donor Intestinal Transplantation
- ▶ Intestinal and Multivisceral Transplantation: The Operation
- ▶ Pathology of Intestinal Transplantation

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Pathology of Intestinal Transplantation

Phillip Ruiz

Contents

Abstract

The transplant pathologist's role in monitoring potential complications occurring within alimentary track transplants is a critical component of the clinical team during their management in the critical posttransplant period. Though there has been only approximately two decades of successful human bowel transplantation, enough progress has been made in the anatomic pathology evaluation of biopsies from transplanted intestine that interpretations of these typically minute and superficial mucosal tissues yields important information as to the status of the graft went done by an experienced pathologist. While routine morphologic evaluations of these paraffin embedded biopsies lends to a relatively specific diagnosis in many cases, the incorporation of critical immunohistochemical and molecular adjunct evaluations of the tissue holds high promise of notably refining and providing a much more specific diagnosis. As such, today's transplant pathologist must go beyond the microscope

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and be well versed in these new and evolving areas, as well as the clinical medicine associated with these patients, so that a proper integration of all results provides a comprehensive and thorough interpretation.

Keywords
Transplantation · Small bowel · Allograft rejection · Pathology

Introduction

Short Gut Syndrome (SGS) and substantial gastrointestinal failure therapy secondary to a variety of causes has advanced over the last 25 years with the application of intestinal and multivisceral transplantation (Lacaille 2012). As described in other chapters, continued experience has been important to an improvement in graft and patient survival with these organ transplants (Fishbein 2009). Pediatric and adult patients can both receive alimentary tract grafts, and there are variations in the surgical procedure for intestinal transplantation (e.g., isolated intestinal allograft [ITx]; multivisceral transplant [MVTx]) (described in other chapters).

The introduction of an intestinal or multivisceral graft into a recipient represents a massive lymphoid and nonlymphoid cellular load to the recipient, which for the most part is histoincompatible and potentially immunogenic; this in return necessitates significant use of powerful immunosuppression in order to maintain the viability of the grafts in the face of a sustained and dynamic immune-mediated attack from the host. The ensuing immunosuppressed state places the organ recipient at risk for the development of malignancies and infections, as well as the potential for direct toxicities on several organ systems by the drugs themselves (Naesens et al. 2009). While an improved understanding of intestinal graft rejection mechanisms has allowed the design of interventional protocols that often now protect the recipient and graft from immunologically based injury, the frequency of alloimmune-based host-derived immune response and sometimes the graft immune response to the host (i.e., Graft vs. Host Disease or GVHD) (Wu et al. 2011) in ITx and MVTx remains very high. Aside from the level and type of immunosuppression, other variables such as the type of host innate genetic polymorphisms present that may influence the level of host responsiveness (Fishbein et al. 2008), the ratio of effector to regulatory cell populations (Wood and Goto 2012), and the degree and type of genetic disparity between the host and donor affect the host alloimmune response. In addition to immune system misalignment, factors such as pre- and posttransplant alimentation protocols, previous abdominal surgeries, and co-morbidities associated with the underlying disease(s) of the host are important influences. Please see below a list of some of the complications experienced in alimentary graft transplants.

List of potential complications after intestinal transplantation

Acute rejection
Chronic rejection
Infection
PTLD
GVHD
Renal dysfunction
Bowel perforation
Pancreatitis
Anastomotic leakage
Others

The transplant pathologist, whether by biopsy evaluation and/or coordination of laboratory analysis, occupies a central role in the clinical team's vigilance of potential complications and monitoring of intestinal graft function (Ruiz 2012). Thus, *Transplant Pathology* as related to gastrointestinal transplantation has evolved into a discipline that coordinates traditional histologic biopsy examination with general and specialized clinical laboratory analysis (e.g., histocompatibility lab), comprehension of pathophysiological mechanisms associated with allograft intestine or the other transplanted abdominal viscera with knowledge and implementation of developing molecular techniques (Ruiz 2009).

In the case of MVTx, the transplant pathologist is required to have an expanded knowledge of

surgical allografts not characteristically encountered (i.e., stomach, colon) and a cognizance of the spectrum of pathological changes contingent upon which area of the gastrointestinal tract is sampled (e.g., duodenal vs. ileal) (Koo et al. 2016). In addition to biopsies from transplanted organs, there is often simultaneous obtaining of biopsies from native organs such as esophagus, rectum, and skin. Comparison of native versus allograft tissues is a valuable tool in discerning whether changes are exclusive to alloimmune responses (i.e., rejection), generalized pathologies (e.g., infection, PTLD), or graft-derived changes (GVHD, preservation injury). Biopsies attained of the ostomy site tend to be difficult to interpret since there may be ongoing inflammatory responses reflected by histological inflammatory processes, fibrosis, and distorted architecture, in addition to other complications such as rejection.

Histopathological Evaluations

It is critical that there be a combination of histopathological evaluation of the transplants with clinical laboratory support during all stages of clinical intestinal and multivisceral transplantation, from the pretransplant phases and continuously through the evaluation and maintenance of long-term surviving grafts (Remotti et al. 2012; Ruiz 2012). Most tissue samples taken from selected regions of ITx and MVTx allografts are visualized by endoscopy, and sampling of mucosal areas is the typical tissue that is procured. Biopsies from intestinal and gastric allografts are technically obtained in a fashion similar to biopsies from the native organ counterparts. It is essential that the experienced transplant endoscopist and transplant pathologist maintain communication in order to optimize interpretation of the graft and/or native tissue. As with biopsies obtained from any transplanted organ, it is imperative that the transplant pathologist has a reasonable clinical history of the recipient (e.g., date of transplant, native disease or problem that necessitated the transplantation, current clinical symptoms), what were the previous biopsy results (if any), and as mentioned above, an impression of the endoscopic appearance of the organ. Due to gastrointestinal transplant complications having high clinical urgency with the capacity to rapidly lead to allograft dysfunction and potential graft loss, processing and evaluation of allograft biopsies must be expeditious (e.g., two-hour turnaround time for permanent sections) and available 7 days a week. The histology lab and pathology service processes biopsy fragments that were immediately placed in an appropriate fixative (typically buffered formalin), and paraffin sections are typically cut at 0.5 cm with multiple levels since processes such as rejection may be geographically limited and not diffusely distributed. In addition to initial Hematoxylin and Eosin (H&E) stains used for the initial evaluation, specialized immunohistochemical (IHC), immunofluorescence (IF) (e.g., to infectious agents such as CMV, adenovirus), and in situ hybridization (ISH) techniques (e.g., EBV) are also often needed. The transplant pathology lab should also serve as an initiation point for graft tissue-derived molecular assays such as quantitative infectious agent evaluations, antigen receptor rearrangement studies for T and B cells, and specific gene arrays.

Donor Organ Pathology and Preservation Injury

As with other solid organ transplants and described in other chapters, procurement of intestinal or multivisceral donor organs from deceased individuals depends upon on a complex but coordinated system whereby potential donors fit certain criteria for the potential recipient (Ueno and Fukuzawa 2010). In the case of intestine or other abdominal viscera, gross surgical inspection of the donor organs during retrieval suffices to assess any possible lesions; rarely, frozen section evaluation by a pathologist is needed for ITx or MVTx. Concurrently, the testing laboratory must rapidly provide a wide-ranging battery of tests for assessing potential infectious pathogens in the proposed donor, and the clinical team must try to identify the status of the donor organs insofar as issues such as ischemic injury, possible tumors, and ongoing medical conditions that could

compromise gut function. The pathological evaluation of residual donor tissue has typically not shown any significant pathological changes aside from ischemic injury, as would be expected from graft preservation.

As separately described, there is typically minimal "cold ischemic" time associated with gastrointestinal grafts although there is almost always some degree of preservation-associated or ischemia reperfusion (I/R) injury to the allograft (Eltzschig and Eckle 2011). Ischemia/reperfusion injury in the gut (Mallick et al. 2005) results in a surge of physiological alterations of assorted genes that could ultimately influence the function of the allograft.

Following transplantation, ITx and MVTx transplants are frequently examined with "protocol" biopsies, particularly in the initial weeks posttransplant; during this period, it is not unusual for mucosal biopsies to demonstrate preservation injury changes (Quaedackers et al. 2000). Intestinal transplants undergoing mild preservation injury tend to demonstrate diffuse edema and swelling of the villi without a significant increase in the inflammatory cell infiltrate, some vascular congestion, and a separation of the surface epithelial lining from the underlying lamina propria (Fig. 1). Severe I/R injury is clinically evident and can show epithelial cell necrosis extending from the surface of the mucosa to the deep submucosa verified in experimental models of I/R injury (Beuk et al. 2008). Presently, the morphology of stomach allografts undergoing I/R injury is not well described.

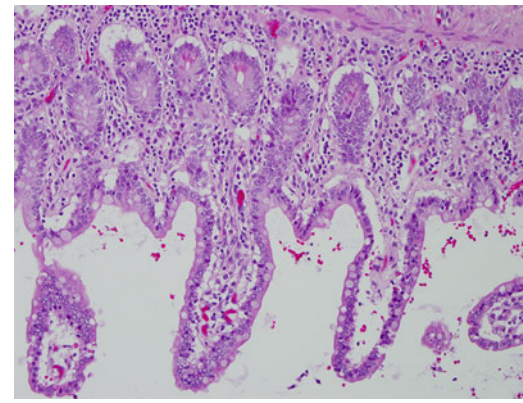

Fig. 1 Preservation injury (original magnification x200, H&E): Small intestinal biopsy several days after transplant shows swelling of the villi without a significant increase in the inflammatory cell infiltrate, some vascular congestion, and a separation of the surface epithelial lining from the underlying lamina propria

Acute Rejection

The genesis of alloimmune effector processes includes the orchestration of expanded recipient alloimmune lymphoid cell populations (cell mediated or T-cell rejection), host B cell-derived alloantibodies (humoral or antibody-mediated rejection), and nonspecific innate immune mechanisms. When these processes remain uncontrolled by regulatory processes or immunosuppression, they represent an assault of antigraft inflammatory responses that clinically, physiologically, and pathologically is expressed as *acute rejection* (Wood and Goto 2012). Depending upon their combinations with each other, immune-based cell populations and soluble immune molecules responding to the graft yield different clinical and pathological manifestations of "injury" that have classically been delineated morphologically and sometimes behaviorally as distinct forms of acute rejection. Since unabated acute rejection reduces graft function and leads to organ loss, the detection and effective interruption of acute rejection in ITx and MVTx recipients, as with other solid organ transplants, remains a consistent goal for transplant clinicians. However, in spite of the application of powerful immunosuppressive drugs, allograft acute rejection remains as an important and common complication in GI transplantation. The pathophysiological mechanisms involved in T cell-mediated and antibody-based forms of acute rejection are similar to other solid organ alloreactive combinations and beyond the scope of this chapter. Fundamentally, recipient-derived B cells and T cells (the principal cells representing the adaptive immune response), in a complex interplay with innate immune populations (e.g., natural killer cells, dendritic cells, macrophages) (Asaoka et al. 2011), participate in the recognition and injury to the allogeneic GI tissue. There are multiple potential cellular

targets in gastrointestinal tissue for immune effector cells and molecules that when injured leads to fever, malabsorption, dysmotility, and ischemia. Acute rejection of the bowel can progress rapidly and in some circumstances can lead to exfoliation of the mucosa and submucosa (Kato et al. 2004; Park et al. 2010), transmural ischemia, and predisposition to translocation of luminal bacteria, the latter scenario evolving to sepsis.

Clinical and endoscopic correlation is critical when considering the potential diagnosis of acute rejection. Bowel acute rejection can be associable with an assemblage of symptoms that can include increased fecal output (early on from their stoma), fever, and swelling (Tzakis et al. 2005); these symptoms however are not specific. Morphologically defined acute rejection in the absence of clinical symptoms is acknowledged as *subclinical rejection* (SCR), and this entity has been described in bowel allografts (Takahashi et al. 2007), comparable to several other solid organ transplants including liver and kidney. SCR is usually detected when biopsies are taken as part of protocol surveillance and the patients are clinically stable; it is potentially an important entity since patients with it may be at risk of a greater rate of eventual graft loss, and some protocols treat SCR with additional immunosuppression. Adjunct noninvasive lab and biomarker assays, though currently lacking optimal specificity and sensitivity, are growing in use in order to further support a morphological diagnosis of acute rejection on the biopsy (Mercer 2011). These tests include cytofluorographic analysis of peripheral immune cell populations, cytokine profiling, and the quantitation of distinct gene set changes (Asaoka et al. 2011). Blood levels of the amino acid citrulline, though not specific for rejection, provide an assessment of viable intestinal mass (Ruiz et al. 2010c). However, specificity in detecting acute (or chronic) rejection with adjunct biomarkers alone does not appear possible. Currently, histopathological examination of GI allograft biopsies remains as the most reliable and definitive method to diagnose rejection.

Morphology: The histopathology associated with acute rejection in biopsies after ITx or MVTx represents a wide range of changes and fluctuates according to many variables with recipient, graft and time posttransplant. As with other solid organ allografts, the classification of acute rejection in small bowel and multivisceral transplantation utilizes terminology that derives from basic immunology (hyperacute rejection, accelerated acute rejection, acute vascular rejection, etc.) – with time, these terminologies have become more standardized. It is also now increasingly recognized that morphological changes associated with these subtypes of acute rejection also appear to be able to coexist (i.e., "mixed rejection"). Despite that, a general classification is currently utilized that is based on the general underlying etiology of the rejection that being antibody-mediated or T cell-mediated but with the caveat being that all forms of rejection can coexist and that this is a frequent situation.

Antibody-Mediated Rejection (AMR)

Hyperacute and Accelerated Acute Rejection

Hyperacute and accelerated acute rejection are terms that outline the situation infrequently encountered in which an allograft organ is exposed to extremely high levels of preformed alloantibodies that cross react with antigens on the organ (i.e., donor-specific antibodies) and is subsequently severely rejected within minutes to hours (*hyperacute rejection*) or a few days (*accelerated acute rejection*) following implantation. These potentially devastating forms of acute rejection occur almost exclusively in the presensitized patient (i.e., preexisting antibodies) and result in a severe antibody-mediated response in which the vasculature endothelium is the principal target, characterized histologically by vascular injury, thrombosis, and ischemic lesions. Clinical cases of hyperacute rejection in ITx or MVTx have been described (Ruiz et al. 2010a). The scarcity of hyperacute or accelerated acute rejection is a testament to the prognostic success of cross-matching of recipient sera by the histocompatibility lab with donor cells before GI transplantation; pretransplant crossmatching was

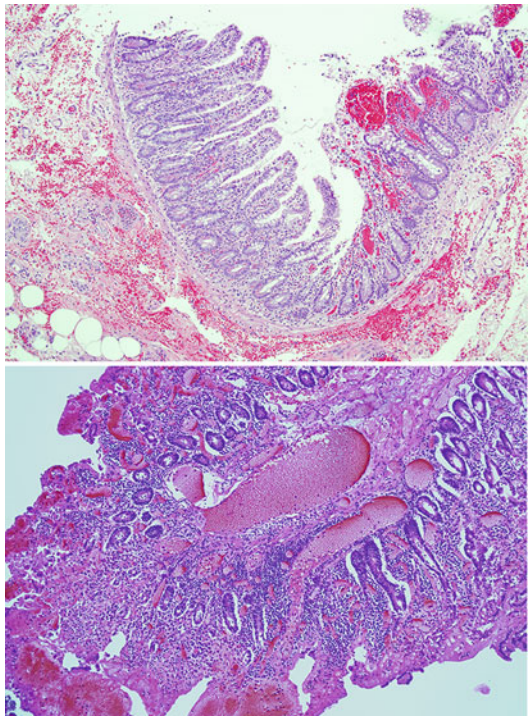

Fig. 2 Hyperacute rejection (original magnification 400x, H&E). Representative changes of bowel allograft on Day 2 posttransplant undergoing hyperacute rejection due to high level of donor specific alloantibodies bowel. There is marked hemorrhage, vascular congestion, and mixed inflammatory cell infiltrate. Inflammatory cells were within several arteries

historically not the norm although that has notably changed in recent times.

Grossly, the donor graft upon anastomosis immediately turns dusky in color and becomes hyperemic, resembling changes seen in other solid organ grafts experiencing hyperacute rejection. The histopathological changes seen with hyperacute rejection of intestine include extensive mucosal congestion and necrosis with mixed acute inflammation and neutrophilic margination around vessels (Fig. 2). There is diffuse and severe vascular congestion with erythrocyte extravasation that extends from the mucosa through the entire thickness of the graft (transmural). Frank arteritis is seen and native tissue tends to be unremarkable.

Curiously, these patients have the capacity to overcome this severe form of antibody-mediated acute rejection if there is aggressive intervention with plasmapheresis, treatment with anti-CD20 antibody (among other immunosuppression) and close monitoring. One of these patients with hyperacute rejection exhibited a full salvage of bowel graft function (normal graft morphology and asymptomatic) that coincided with reduction of titers of antidonor antibodies and normal endoscopic appearance (Ruiz et al. 2010a). On occasion, accelerated AMR occurs in the first several days following small bowel or multivisceral transplantation in which the recipients were sensitized with preexisting alloantibodies and that morphologically demonstrated features of AMR described below, but not to the degree seen for hyperacute rejection.

Acute Antibody-Mediated (Humoral) Rejection (AAMR)

As an entity, AAMR in human small bowel and multivisceral transplantation is acknowledged as an important cause of graft injury and dysfunction. AAMR originates with antibodies (Parekh et al. 2016) directed to alloantigens that then initiate a cascade of inflammation, coagulation, and other events that directly injure the transplant. Consequently, identification of AAMR cannot be accomplished as a form of rejection without additional histochemical techniques and evidence of pre- and/or posttransplant alloantibody. Inflammation of arteries (vasculitis) can be one of the histological components of AAMR; however, this is not specific to antibodies since the cell-mediated arm of the immune response (T-cell-mediated vasculitis) can also be an underlying cause of vasculitis in bowel allograft vessels. Severe forms of AAMR in small bowel transplants are often associated with alloantibody posttransplant sensitization of the recipient to donor antigens and subsequent rises in titers of pretransplant antibodies that were present at very low amounts before the transplant. The graft often demonstrates widespread inflammatory changes with a critical lesion being vasculitis of large to small arterial branches (Fig. 3). The vasculitis tends to show intimal edema and endothelial cell reactivity with an infiltration of acute and chronic inflammatory cells in the intimal layer of the artery.

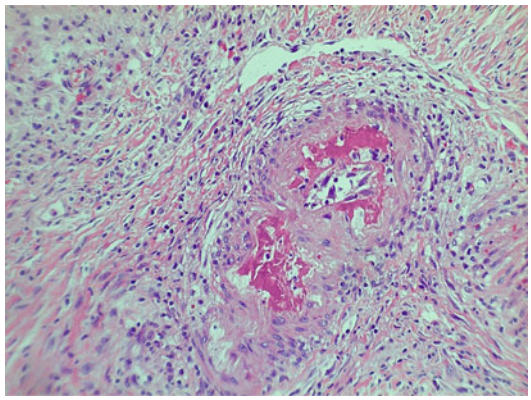

Fig. 3 Acute antibody-mediated rejection – vasculitis (original magnification x400, H&E): Representative medium sized artery in the submucosa of an intestinal allograft at day 25 posttransplant with high levels of donor-specific alloantibodies

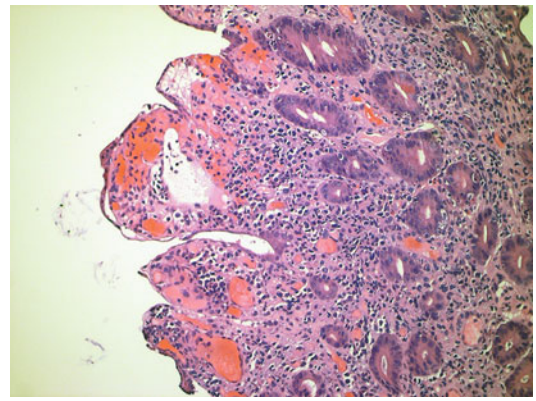

Fig. 4 Acute antibody-mediated rejection (original magnification x400, H&E): Extensive vascular congestion of mucosal vasculature in patient with high levels of donor-specific alloantibodies. The interstitium also displays notable enteritis with epithelial apoptosis signifying concomitant acute cellular rejection

There are variable amounts of deposited complement components (e.g., C4d and C3d) and fibrinogen in lamina propria vasculature and larger vessels. Left unimpeded, the vasculitis can evolve to transmural inflammation with fibrin deposition and necrosis of the artery, causing severe ischemic injury to the graft. Occasionally, selective arteries in the graft can be affected more severely than others by the vasculitis. For example, mesenteric arteries can undergo AAMR and this can lead to sclerosing mesenteritis (Ruiz et al. 2003b). Severe vasculitis can also be evident in stomach and colon allografts with patterns as seen in the small bowel. When considering a differential diagnosis for this form of severe vasculitis only involving the transplant, other causes such as infectious agents (such as fungal or viral agents), neoplasia, drugs, and autoimmune processes should also be considered, although these are not common causes and characteristically would be distributed in native organs as well as the allograft. Vasculitis tends to be relatively infrequent in mucosal biopsies; thus, the diagnosis of AAMR based upon severe vasculitis lesions in mucosal biopsies can be challenging in small bowel transplants.

AAMR often occurs in less severe forms in small bowel, stomach, and colon transplants and alterations identifying early, mild, or evolving AAMR that can be isolated or occur in conjunction with T cell-mediated acute rejection have been described (Ruiz et al. 2003a). These early and/or mild forms of AAMR appear associated in many cases with preexisting or posttransplant alloantibody formation with subtle, yet consistent mucosal morphological changes, often in the early period after transplantation. There is mild to diffuse, substantial vascular congestion with erythrocyte extravasation of the villous region and lamina propria microvasculature of the allograft mucosa (Fig. 4), and there may be no evidence of any significant vasculitis. There are various grades of congestion in the vasculature that can be graded. In suspected AAMR cases, an immunofluorescence or immunohistochemical panel for the presence of immunoglobulins (IgG, IgA, IgM) and complement components (C3, C4, C1q); fibrinogen, C3d and C4d can be useful In AAMR, there can be immunoglobulins deposited along vessels and within interstitium along with complement components. In the presence of C4d, C3d may be found in small arteries and small capillaries in patients with milder or evolving forms of AAMR as in other transplanted organs and GI transplants undergoing severe antibody-mediated rejection (mentioned above) (Fig. 5). At this point, these subtle forms of AAMR do not demonstrate specific histopathological findings and some of these alterations can be found in

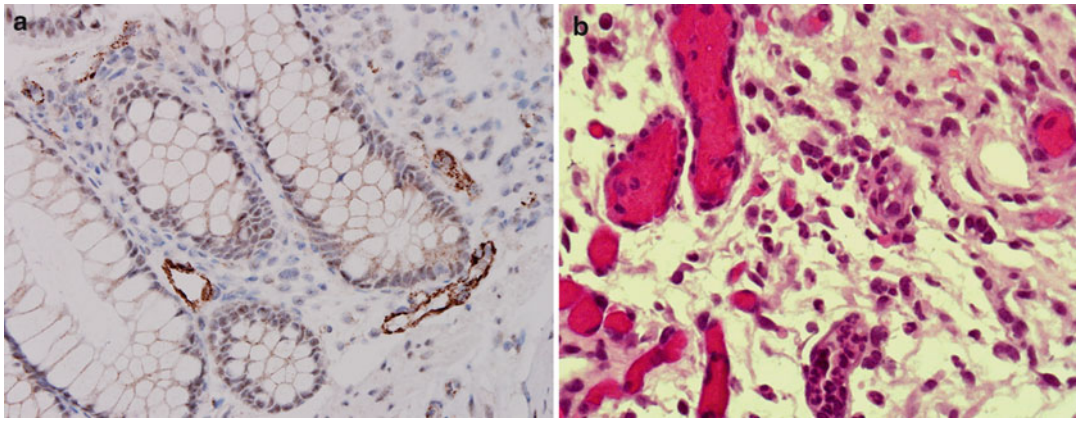

Fig. 5 (**a**) Acute antibody mediated rejection (original magnification x400). Graft undergoing antibody-mediated rejection with H&E showing significant vascular congestion and neutrophilic margination. (**b**) Immunohistochemical staining for C4d in the same biopsy shows positive staining of the microvasculature of the mucosa

ischemia, nonspecific enteritis, viral infections, and mechanical vascular problems. Therefore, it is essential to incorporate the clinical history and lab values (e.g., alloantibody antidonor titers), lesion distribution (allograft versus native tissue), other morphological findings (e.g., the presence of an acute inflammatory cell infiltrate or superficial epithelial changes with enteritis), and culture results. Furthermore, there should be a relationship of symptoms and histopathological resolution with supplemented immunosuppression concomitant with reduction of alloantibody concentrations.

Acute T-cell-Mediated (Cellular) Rejection

Acute T-cell mediated rejection (ACR) is the most commonly recognized form of acute rejection in gastrointestinal (and other solid organ) transplants and can occur with other forms of rejection and/or other complications. The recipient's T-cell-mediated response to donor alloantigens underlies this form of rejection which is histologically characterized by a mixed, lymphocyte-rich chronic inflammatory cell infiltrate principally dispersed within the interstitial regions of organs and injuring of specific tissue parenchyma substructures (Lee et al. 1996). Targeted cellular elements include crypts, glandular structures, as well as muscle, endothelial and nerve cells. Functional and structural sequelae from this injury to the parenchyma can include metaplasia, apoptosis, and altered regulation of cell pathways.

Vascular compromise from the T-cell-based alloimmune effector cell-based injury to the vessels can lead to general necrosis. The process of ACR in gastrointestinal allografts is multifactorial and results in in epithelial cell apoptosis (Delacruz et al. 2004) (Figs. 6 and 7) that appears principally due to CD8+ cytotoxic T cells, induction of target cell apoptosis via the Granzyme B/Perforin-dependent granule-exocytosis pathway, and Fas and Fas ligand–mediated cytotoxicity (Asaoka et al. 2011). Non-CD8+ T cells also seem to potentially contribute to crypt epithelial cell apoptosis and acute allograft rejection in experimental animal models.

Regional differences in the gastrointestinal tracts exist insofar as susceptibility to ACR; for example, the ileum displays ACR more commonly and frequently more severely than duodenum or jejunum (Takahashi et al. 2006). There may be severe infectious complications as a consequence of the heavy immunosuppression to treat ACR and alloimmune-mediated injury and impairment of mucosal barrier function (intestinal epithelial cells, intercellular tight junctions, and basement membranes) can result in bacterial translocation into the peritoneal space (Zou et al. 2005).

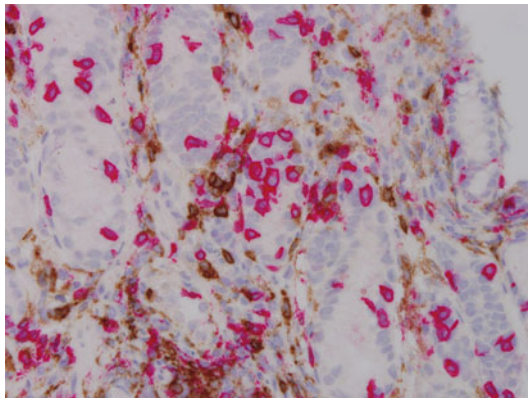

Fig. 6 Acute T-Cell Mediated Acute Rejection (original magnification 400x, two color immunohistochemistry to CD4 and CD8): Two color staining of gastrointestinal graft biopsy undergoing Acute T cell mediated rejection, with CD4 (*brown*) and CD8 cells (*red*) within the interstitium and infiltrating glands. The CD4: CD8 ratio overall was estimated at 1:3

Several classification schemes for grading acute T-cell-mediated rejection (ACR) in small bowel/colon transplants have been described (Lee et al. 1996; Wu et al. 2003), as well as a classification system for stomach (Garcia et al. 2004). A unified grading scheme for ACR in small bowel allografts was first developed in 2003 at the Eighth International Small Bowel Transplant Symposium by an international group of pathologists and clinicians experienced in small bowel transplant morphology (Ruiz et al. 2004a) (Table 1). This scheme is now widely used and has been employed at the University of Miami for greater than 5,000 biopsies (Ruiz et al. 2010b). To date, there appears to be good correlation between the morphological grading system and the clinical symptoms displayed by the recipient as well as with interobserver studies between different institutions (unpublished data).

No Evidence of Acute Rejection, Grade 0

The changes associated with this grade are essentially minimal or none (i.e., histomorphology is indistinguishable from normal bowel) in regards to acute rejection; however, other concurrent conditions (nonrejection) may be present (Fig. 8).

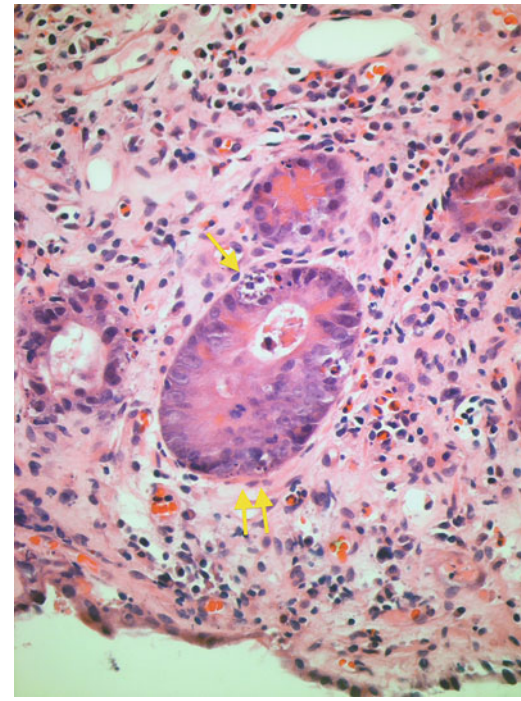

Fig. 7 Apoptosis in bowel allograft (original magnification x400, H&E): Bowel crypts demonstrating several forms of apoptosis of lining epithelial lining cells including larger "popcorn" type of apoptosis (*single arrow*) and the more subtle forms of cellular degeneration (*two arrows*). Inflammatory cells are also infiltrating the gland

Indeterminate for Acute Rejection, Grade IND

The morphological alterations apparent in biopsies with this grade can be seen at any stage including the early or resolving stages of ACR when there is a minor amount of epithelial cell injury or destruction, but there is an added inflammatory infiltrate within the parenchyma. The inflammation tends to be composed of lymphocytes, eosinophils, immunoblasts, some plasma cells, and occasional neutrophils, with varying proportions and with the diffuse or focal intensity being visibly increased above normal (Fig. 9). Simultaneously, there is frequently also villous blunting, edema, and vascular congestion present although these features are not obligatory for the diagnosis. Cryptitis with lymphocytes or eosinophils and epithelial apoptotic bodies may be present. However, the number of apoptotic bodies

Table 1 Characteristics of acute cellular rejection in small intestinal allograft

Grade	Score	Description	Histopathological findings
0	0	No evidence of acute rejection	Unremarkable histological changes that are essentially similar to normal native intestine
IND	1	Indeterminate for acute rejection	A minor amount of epithelial cell injury or destruction; increase in crypt epithelial cell apoptosis, but with less than six apoptotic bodies per 10 crypts; increased inflammatory infiltrate in lamina propria, mixed but primarily mononuclear inflammatory population; edema, blunting, vascular congestion can be present
1	2	Acute cellular rejection, Mild	Altered mucosal architecture (e.g., mild blunting of villi), edema, vascular congestion; increased crypt epithelial cell apoptosis (six or more apoptotic bodies per 10 crypts); increased inflammatory infiltrate in lamina propria, mixed but primarily mononuclear inflammatory population with blastic and activated lymphocytes
2	3	Acute cellular rejection, moderate	Features of Grade 1 as well as multiple; markedly increased crypt epithelial cell apoptosis (six or more apoptotic bodies per 10 crypts), accompanied by foci of "confluent apoptosis"; whole gland necrosis and/or crypt abscess; extensively increased inflammatory infiltrate in lamina propria, mixed but primarily mononuclear inflammatory population with blastic and activated lymphocytes; edema, vascular congestion, and blunting of villi of higher degree of Grade 1
3	4	Acute cellular rejection, severe	Extensive morphological distortion and crypt damage with apoptosis, gland destruction, and associated mucosal ulceration; marked diffuse inflammatory infiltrate with blastic and activated lymphocytes, eosinophils, and neutrophils; granulation tissue and/or fibropurulent exudate with mucosal sloughing ("exfoliative rejection")

does not reach the level designated for grade 1 (mild) ACR.

Acute T-Cell Mediated Acute Rejection (ACR), Mild, Grade 1

Mild ACR (grade 1) demonstrates the crypt cell injury, inflammation, and all the other changes ascribed for the *Indeterminate* category (grade IND) but at higher levels, including the level of apoptosis. Classification of mild ACR necessitates six apoptotic bodies or above per ten crypts as the minimal cutoff, as designated in the International Grading Scheme (Ruiz et al. 2004a); other features typically include edema, congestion, and altered architecture such as villous blunting. The mixed chronic inflammatory cell infiltrate is mild to moderate intensity and inclines being diffusely distributed (Figs. 10 and 11), often with deeper extension to the submucosa and muscle. All of these morphological features, particularly the character and intensity of the infiltrate, can fluctuate according to the time after transplantation and which therapy is be utilized for treatment of the ACR. Regenerative features such as mucin loss, epithelial cell nuclear enlargement, and hyperchromasia may also be present, contingent on the duration of the rejection. Vascular congestion and endothelialitis may be present with this and higher forms of ACR.

Acute T-Cell Mediated Acute Rejection (ACR), Moderate, Grade 2

ACR, moderate (grade 2) shows the features of mild ACR but with intensified crypt cell injury such that multiple and confluent apoptotic bodies are evident in single crypts. There may be whole gland necrosis and crypt abscesses. The inflammatory infiltrate in the lamina propria and submucosa is more severe than with mild ACR, and the nature of the infiltrate is mixed but predominantly being a mononuclear inflammatory cell population, including blastic or activated lymphocytes and mucosal architectural alteration tends to be significant. The moderate to severe intensity infiltrate is seen in spite of the time after transplantation, and villous blunting, edema, and vascular congestion are inclined to be more widespread with this higher degree than with grade 1 rejection (Figs. 12 and 13).

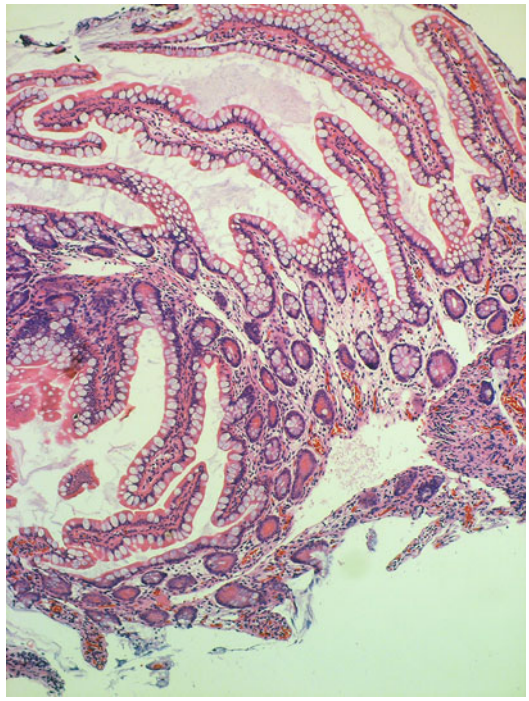

Fig. 8 No evidence of acute rejection (original magnification x200, H&E): Small bowel allograft 7 days post-transplantation and showing no evidence of any significant alterations associated with acute rejection. Overall, the hematopoietic cell levels are less than seen with other immunosuppressive therapy

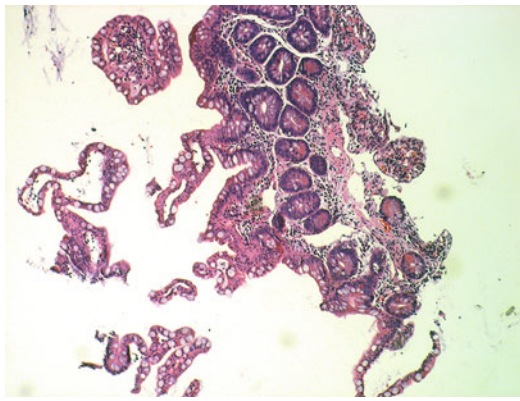

Fig. 9 Indeterminate for acute rejection, Grade IND (original magnification x100, H&E): Small bowel allograft with a subtle yet increased interstitial inflammatory infiltrate composed of lymphocytes, eosinophils, immunoblasts, some plasma cells, and occasional neutrophils along with mild blunting of villi

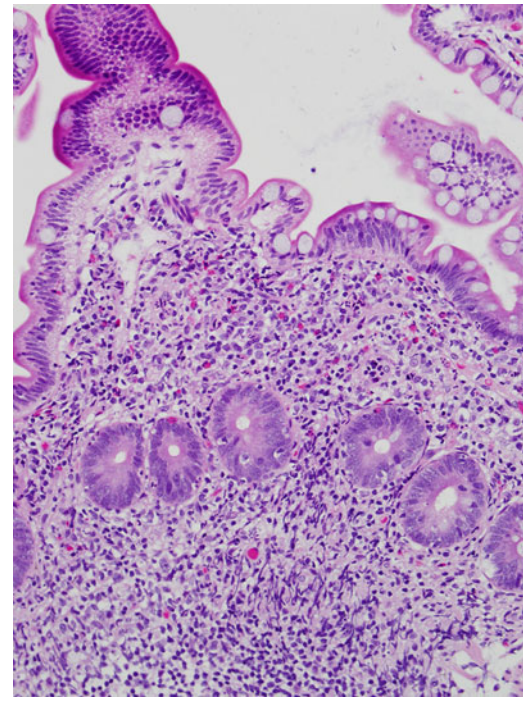

Fig. 10 Acute cellular rejection, mild (grade 1) (original magnification x200, H&E): Mixed inflammatory infiltrate and several apoptotic bodies are seen in crypts (greater than 6 apoptotic bodies in 10 crypts)

Acute T-Cell Mediated Acute Rejection (ACR), Severe, Grade 3

Severe (grade 3) ACR can be clinically disastrous, and although T cell mediated rejection is central to this type of rejection, there is often also an allo-antibody-mediated component and it can be considered a "mixed" acute rejection (ACR plus AAMR). Crypt cell injury and apoptosis, gland destruction, and related mucosal ulceration are frequent features. The level of crypt epithelial apoptosis is variable; in fact, there may be a normal level of apoptosis among the surviving crypts, the latter that are often in a regenerative state. There is a marked diffuse inflammatory infiltrate with blastic or activated lymphocytes, eosinophils, and neutrophils. The tissue is often friable, and only fragments of tissue with significant architectural alterations may be obtained. Prolonged severe rejection can result in complete loss of the bowel histological architecture, and there may be predominantly granulation tissue

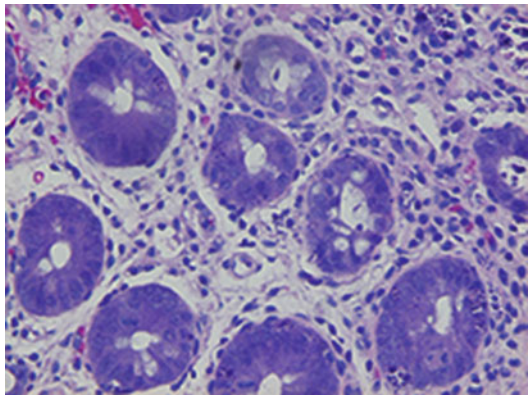

Fig. 11 Acute cellular rejection, mild (grade 1) (original magnification x400, H&E): High magnification representation of inflammatory infiltrate and epithelial cells within crypts undergoing extensive apoptosis

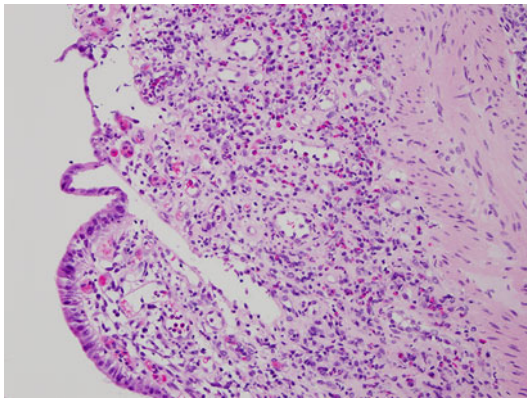

Fig. 12 Acute cellular rejection, moderate (grade 2) (original magnification x200, H&E): Moderate to severe intensity, mixed inflammatory infiltrate with focal attenuation of surface epithelial lining and dilated vasculature with PMN margination; apoptotic bodies were seen in crypts (greater than 6 apoptotic bodies in 10 crypts)

and/or fibrinopurulent (pseudomembranous) exudate, with mucosal sloughing (Fig. 14). Since mucosal ulceration can different etiologies (e.g., ischemic and infectious processes), lesions not also having active crypt cell injury should initially be classified as "consistent with ACR, severe." The culmination of extensive severe rejection resulting in only sloughed, necrotic tissue has also been characterized as "*exfoliative rejection*" (Park et al. 2010). Therefore, it is very useful to obtain tissue obtained from areas that grossly

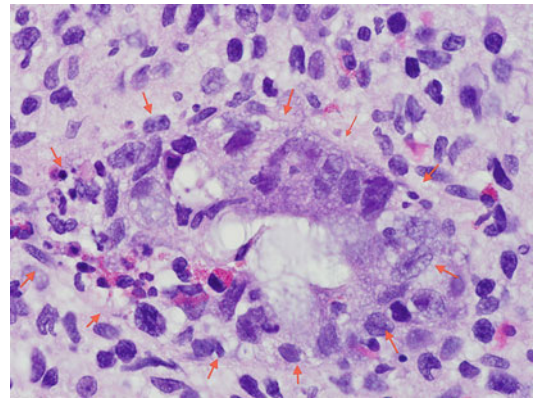

Fig. 13 Acute cellular rejection, moderate (grade 2) (original magnification x1000, H&E): High magnification photomicrograph of crypt undergoing destruction with confluent apoptosis, inflammatory cells (including eosinophils) within the glandular basement membrane. The surrounding inflammatory cell infiltrate is intense in nature and mixed. Arrows delineate the edge of the crypt

appear less involved. Left unabated, severe ACR can lead to intestinal graft loss.

ACR in Colon and Stomach

With multivisceral transplantation, segments of the grafted alimentary tract aside from the small intestine can also be complicated by the occurrence of acute and chronic rejection. The presence of ACR in colon allografts is manifested by comparable changes as seen with small intestine and experience with biopsies from this organ allograft is increasing as colon segments are included more often now with MVTx (Kato et al. 2008). The arrangement and composition of the inflammatory cell infiltrate in colon ACR displays the same pattern as small bowel as well as the epithelial cell injury in crypts (Fig. 15), and the same cell subpopulations appear involved. There can also be architectural distortion, goblet cell loss, and attenuation of the thickness of the surface epithelial cells. The same criteria and grading system are applied for colon as used in small intestine. There is often coexistent native colon in multivisceral transplant patients, and obtaining tissue from native and allograft simultaneously can be useful to the pathologist in distinguishing alloreactive versus other inflammatory processes.

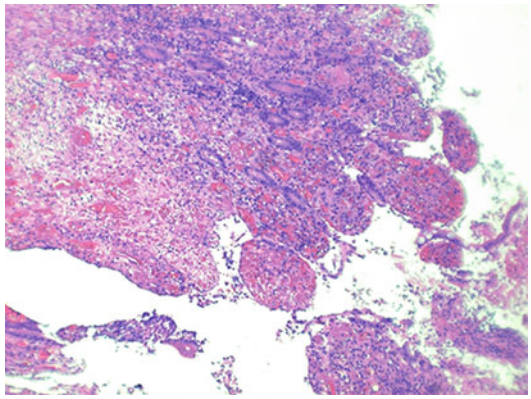

Fig. 14 Acute cellular rejection, severe (grade 3) (original magnification x200, H&E): Mucosal architecture is extensively distorted with "ghosts" of villi, largely replaced by granulation tissue. The evaluation of crypt epithelial cell apoptosis is difficult because of complete loss of crypts. Dense inflammatory infiltrate is seen which consists of mixed, but predominantly mononuclear cell population with blastic and activated lymphocytes, eosinophils, and neutrophils. Marked vascular congestion is evident

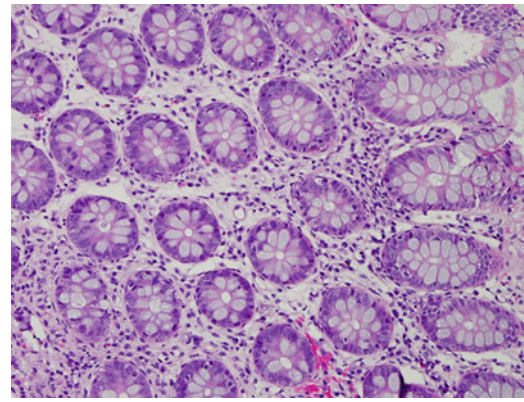

Fig. 15 Acute cellular rejection, mild (grade 1) of colon (original magnification x200, H&E): Mixed inflammatory infiltrate and several apoptotic bodies are seen in crypts (greater than 6 apoptotic bodies in 10 crypts)

Stomach allografts can display ACR in all regions of this organ, exclusively or in combination with other inflammatory processes such as various forms of chronic gastritis and infectious processes. There is epithelial injury in the form of apoptosis and reactive changes, similar to small bowel and colon allografts. There tends to be less degree of inflammation during acute rejection in the stomach compared to intestine such that corresponding grades of acute rejection in stomach do not demonstrate the same level of inflammation and epithelial injury as in small bowel or colon (Fig. 16). However, there are frequent situations where there is isolated gastric rejection or the grades of gastric rejection exceed other regions of the small bowel or colon. A grading scheme for appraising stomach allograft pathology is useful to score individual morphological features (Garcia et al. 2004).

Chronic Rejection

As graft survival progressively improves in ITx and MVTx (Mazariegos 2009; Nayyar et al. 2010), so rises the incidence and recognition of chronic allograft enteropathy (CAE) or chronic rejection of small bowel allografts. Chronic rejection, an important source of late graft loss in gastrointestinal transplantation, originates as with other solid organ transplants, through a complex pathophysiological process, influenced by an interaction of several nonimmune (Murphy et al. 2011) and immune factors (Hirohashi 2012). The nonspecific symptomology (e.g., protein losing enteropathy) for CAE tends to be progressive and unresponsive to therapy, and endoscopic information can include loss of villous structure with flattening; these findings are critical to correlate with the pathological findings of the mucosal biopsies (Figs. 17 and 18). Explanted bowel allografts with severe chronic rejection grossly show a matted organ bloc due to abundant serosal adhesions, with transmural thickening, an irregular flattened mucosal surface, and intermittent ulcerations.

The pathognomonic microscopic lesion of bowel chronic rejection is concentric intimal thickening of small to large-sized arteries with fibrous changes, medial hypertrophy of smooth muscle cells interspersed with foam cells, and adventitial fibrosis (Swanson et al. 2013) (Fig. 19). It is important to note that GI transplant mucosal biopsies are typically limited from being able to demonstrate the large vessel changes of chronic rejection (Perez et al. 2002) since these arteries are not present in these specimens. Occasional chronic inflammatory cells

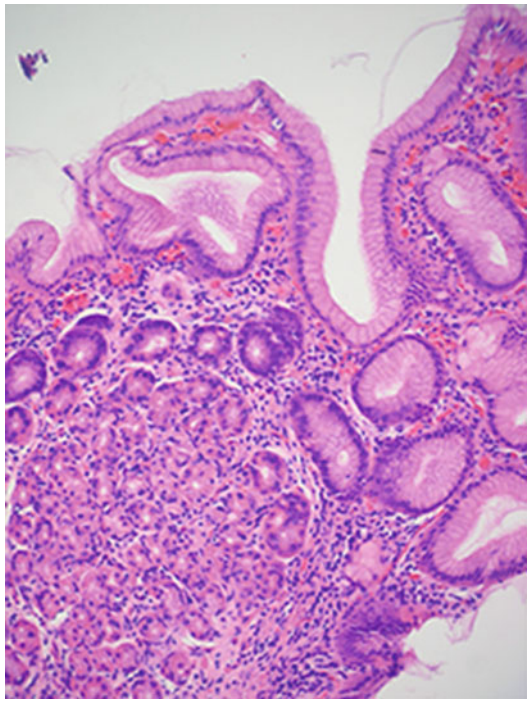

Fig. 16 Acute cellular rejection of stomach (original magnification x100, H&E): Gastric allograft displaying architectural disarray and significant increase of inflammatory infiltrate with epithelial apoptosis. Mild vascular congestion and extravasation are also seen

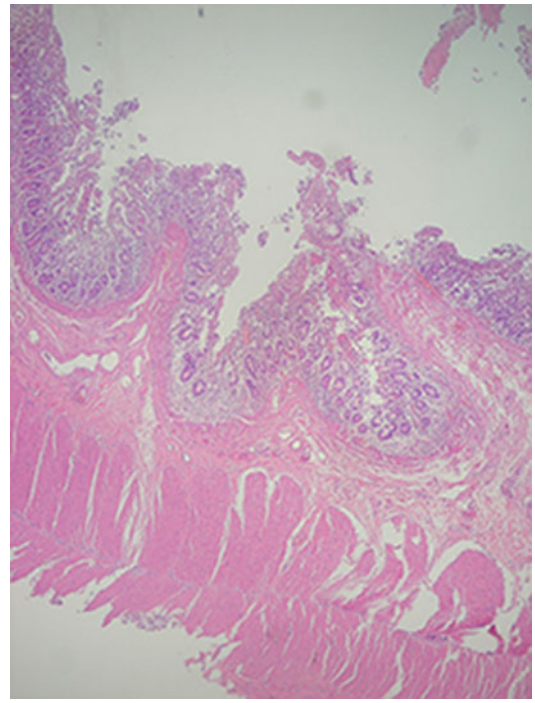

Fig. 17 Chronic rejection of small bowel allograft (original magnification x40, H&E): Explanted bowel undergoing chronic rejection. There is severe fibrosis in the lamina propria and submucosa with loss of crypts

within the intimal space ("active" chronic allograft arteriopathy) or thrombi can be seen in arterial branches undergoing chronic rejection. Fibrosis often involves the mucosal, submucosal, and muscular layers, and there is associated crypt separation and disappearance, epithelial mucin loss, villous blunting, mucosal atrophy, and small arterial branches with evidence of transplant arteriopathy. Other microscopic changes can include ganglion cell destruction and hyperplasia, fibrinous serositis, and chronic inflammation; there may be ulceration and superimposed acute rejection.

Mucosal biopsies from GI allografts with CAE can be very useful in identifying the chronic injury (e.g., fibrosis, crypt loss and distortion, altered architecture) and when incorporated with the clinical and endoscopic history, provide a suspicion for chronic rejection. Appraisal and comparison of adjacent native tissue is very useful since the latter can be unremarkable in CAE. A semiquantitative scoring template for the mucosal biopsy evaluation of chronic rejection along with immunohistochemical characterization of lymphoid and macrophage cell populations is also useful in the identification and prognostication of GI chronic rejection (Perez et al. 2002). To date, no consistently useful biomarkers or gene sets have been routinely used as auxiliary support of biopsies in diagnosing CAE.

Infections

Protracted and high amount of immunosuppression with ITx and MVTx places these transplant patients at risk for several frequent complications, most notably being opportunistic infections (Fryer 2008). These infections can present systemically and/or locally in the graft and adjacent native tissue (e.g., infectious gastritis, enteritis or colitis); unfortunately, these infections can

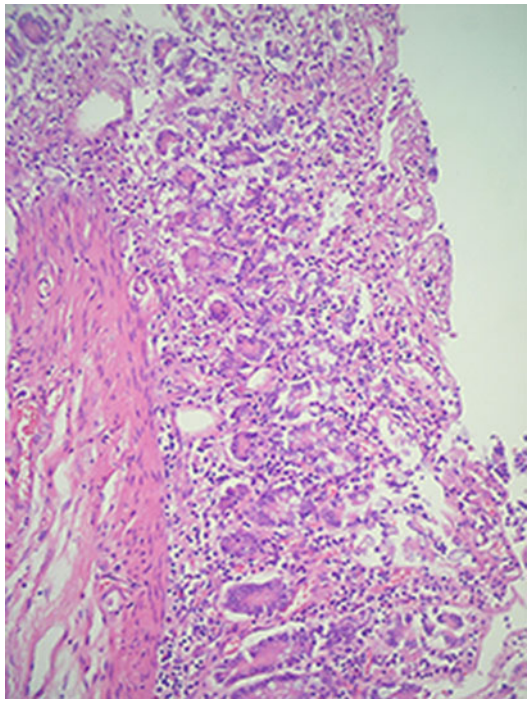

Fig. 18 Chronic rejection of small bowel allograft (original magnification x200, H&E): There is marked architectural distortion and glandular atrophy present

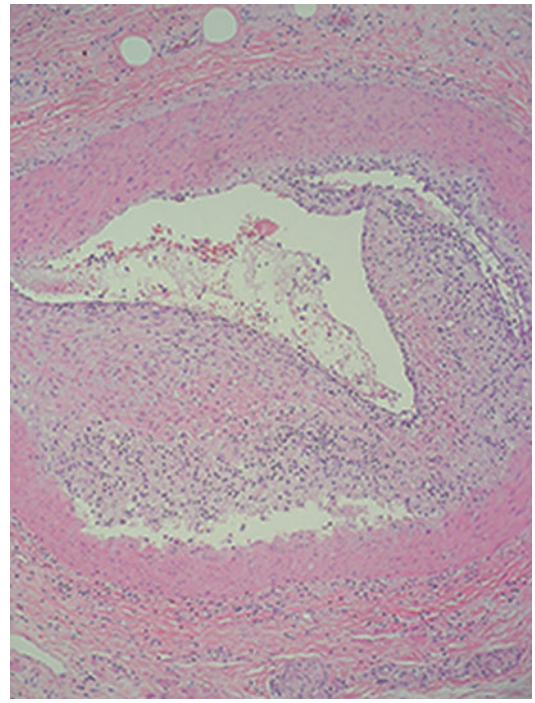

Fig. 19 Chronic rejection of small bowel allograft (original magnification x200, H&E): Marked myointimal hyperplasia and subendothelial accumulation of foamy macrophages and scattered lymphocytes (i.e., "active" allograft arteriopathy) are seen in obliterative arteriopathy in large-sized vessel in the deep submucosa

compromise graft function and place the host at risk of death in the absence of identification and therapy. Since gastrointestinal graft infections with clinical symptoms can sometimes mimic acute rejection (e.g., diarrhea, fever), it must be distinguished by culture, lab testing, and/or biopsy appearance since treatment often includes reduction in immunosuppression.

The GI allograft can be involved by a number of viruses that can have distinguishing histopathological changes and be confirmed by immunohistochemical, culture, or molecular techniques. Among the most frequent viruses are rotavirus, adenovirus, calicivirus (human calicivirus: HuCV), herpes simplex virus (HSV), CMV, and EBV. In general, the presence of these viruses in GI tissue is complemented by an interstitial inflammation (e.g., gastritis, enteritis) (as seen in native organs) that is composed of a varied acute and chronic inflammatory cell infiltrate with focal or diffuse epithelial damage, altered cell proliferation, and cytological changes (Ziring et al. 2005). Necrosis may be apparent, particularly in more severe cases. The presence of a viral infection within the alimentary tract graft can commonly have concomitant acute rejection with one process often exacerbating the other. Thus, it remains important that the transplant pathologist consider the patient's clinical history and culture/molecular test results when evaluating the histology.

Adenovirus infections can be a baffling and perilous complication in GI transplantation, with sporadic reports of cases in ITx and MVTx (McLaughlin et al. 2003). There can subtle or prominent histopathology, sometimes with crypt cell apoptosis and a mixed chronic inflammatory cell infiltrate, disarray of the surface epithelial cells associated with the presence of enlarged, hyperchromatic cells (Fig. 20). Eosinophilic nuclear inclusions as well as "smudge cells"

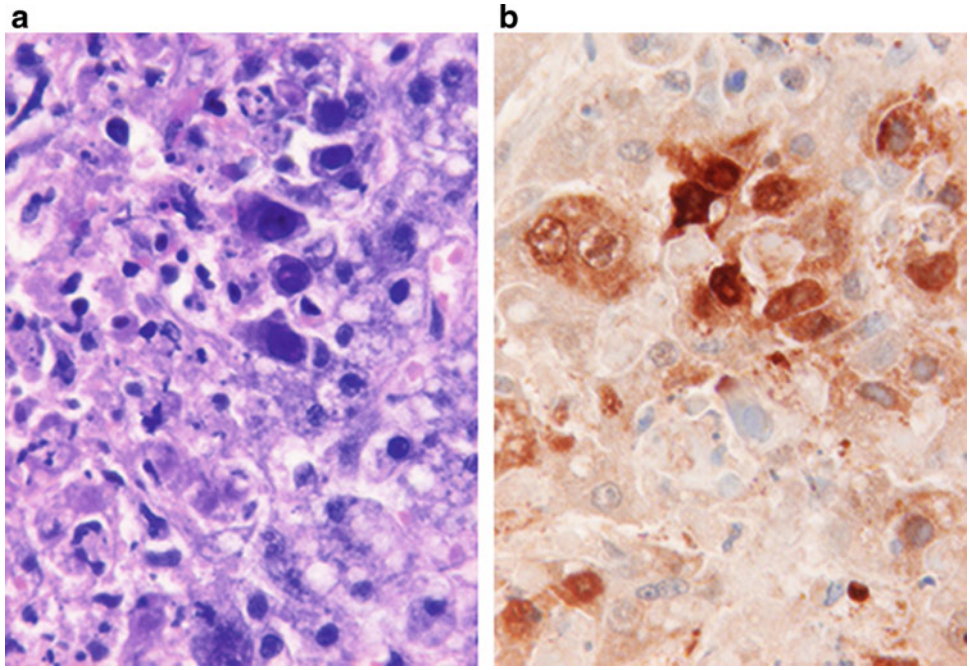

Fig. 20 Adenovirus enteritis (original magnification x400, H&E, Immunohistochemistry): Adenovirus inclusion bodies in small bowel allograft (**a**) and immunohistochemistry demonstrating adenovirus positive cells (**b**)

with enlarged basophilic nuclei and proliferation of surface enterocytes may be evident. Immunohistochemistry, electron microscopy and viral PCR assays (of tissue) for this virus are very useful to help identify the presence of this pathogen. Some of the histopathological changes associated with adenovirus infection can also be evident in acute rejection; therefore, it is critical to use all tools necessary to distinguish the processes. Rapid diagnosis of adenovirus enteritis is essential because without proper treatment the clinical condition of patients can rapidly worsen.

The general pediatric population commonly experiences Rotavirus and it can similarly complicate ITx and MVTx patients. The histopathological alterations associated with this virus are obscure, and biopsies are typically not obtained to identify this pathogen. There may be superficial hyperplastic changes in the epithelium, a mixed mucosal surface inflammatory infiltrate with occasional neutrophils, and cell debris. Deeper crypts tend not to be affected by the epithelial injury. There can be coexistence of acute rejection and rotaviral infections.

Norwalk virus (Norovirus) is another gastrointestinal virus that has been described in intestinal transplant patients (Florescu et al. 2008). There are also a variety of relatively novel viruses that have been identified in human enteric tracts of persons with diarrhea, among them being Caliciviruses, which are nonenveloped, positive-stranded RNA viruses that can cause illness in animals and humans (Farkas et al. 2008). Calicivirus (HuCV) is a common cause of mild gastroenteritis and is composed of two pathogenic strains, Norwalk-like virus, and Sapporo virus. HuCV results in protracted high-volume diarrhea in the general population and is uncovered by RT-PCR in fecal specimens. Histopathological alterations include mixed lymphoplasmacytic infiltrate with a small number of neutrophils in lamina propria, blunting and flattening of villi, disarray and reactive modifications of the superficial epithelium. Vacuolization of the surface epithelial cells can be prominent, and there may be focal erosion. There is also a loss of cellular polarity, increased apoptosis in the superficial epithelium and in the crypts, as well as in macrophages in the

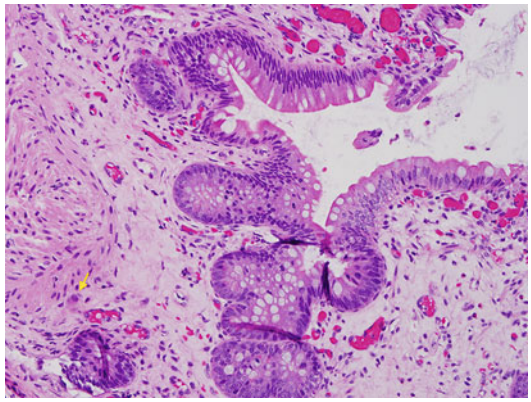

Fig. 21 Cytomegalovirus enteritis (original magnification x200, H&E): Mucosal biopsy showing patchy mixed enteritis with occasional enlarged cells displaying hyperchromatic nuclei (*arrow*) and later shown to be staining positive for CMV by immunohistochemistry. There is concomitant acute cellular rejection, mild (grade 1) with focal erosion, increased vascularity and focal loss of crypts

superficial portion of the lamina propria (Kaufman et al. 2003).

Cytomegalovirus (CMV) infection is among the most common infectious complications in GI transplant recipients (Pascher et al. 2004) and can be systemic or localized in its distribution. When causing enteritis, CMV can present as diarrhea, epigastric pain, and abdominal discomfort. Endoscopic examination can reveal mucosal erosions and ulcers in stomach and in small intestine. Histologically, there can be characteristic large CMV-infected cells with eosinophilic intranuclear inclusions surrounded by a clear halo and thickened nuclear membrane. Intranuclear inclusions can be present in endothelial, stromal, smooth muscle, and epithelial cells often in the presence of a chronic inflammatory infiltrate, composed of lymphocytes and histiocytes, and with neutrophils at times observed in the lamina propria. Isolated intranuclear inclusions are sometimes hidden in dense chronic inflammatory infiltrates and hard to identify (Fig. 21). Immunohistochemical staining for CMV and PCR assessment of tissues for CMV helps confirm the diagnosis of CMV enteritis due to the obscuring at times of severe inflammatory cell infiltrates.

In transplant patients, Herpes Simplex Virus (HSV) infection in the alimentary tract most commonly involves the oral cavity, esophagus, perianal area, and rectum, whereas, HSV enteritis or colitis is relatively infrequent (Gourishankar et al. 2004). HSV enteritis can demonstrate aphthous and necrotic ulcers, mucosal erythema and friability, and inflammatory pseudopolypoid lesions by endoscopy. Microscopically, there is a mixed chronic inflammatory cell infiltrate with lymphoplasmacytic component and scattered eosinophils. Virally infected cells can demonstrate eosinophilic intranuclear inclusions and multinucleation. Simultaneous culturing of the tissue and immunohistochemistry is useful to confirm the diagnosis of HSV enteritis.

Acute Epstein Barr Virus (EBV) infection is uncommon in the ITx and MVTx population, but chronic EBV infection is frequently seen and associated with the development of PTLD (see below).

Among other herpesviruses that are latent but which become reactivated subsequently bearing the capacity to infect and reoccur in intestinal and multivisceral transplant patients include HHV-6, HHV-7, and HHV-8 (Jenkins et al. 2003). HHV-6 is closely related to CMV and can be classified into two classes: HHV-6A and HHV-6B. HHV-6 can be present in ileocolonic mucosa (Sipponen et al. 2011) with immunohistochemical and molecular measurements are often very useful in determining the presence of the virus, which can cause symptoms of gastroenteritis. The histological findings are nonspecific and resemble changes present with a viral infection. Unlike the experience seen in liver transplant patients (Peigo et al. 2009), HHV-7 infection has not been described in bowel (Pascher et al. 2004), although in addition to skin infection and an acute febrile illness, diarrhea has been attributed to acute HHV-7 viremia and infection (Suga et al. 1997). HHV-8 is also known as Kaposi's sarcoma-associated herpesvirus (KSHV) (Cesarman et al. 1995) and can typically can involve solid organ transplant patients by the increased rate of occurrence of Kaposi's sarcoma, primary effusion lymphoma, and Castleman's disease (Ariza-Heredia and Razonable 2011). The Kaposi's sarcoma and lymphoma can primarily affect the bowel.

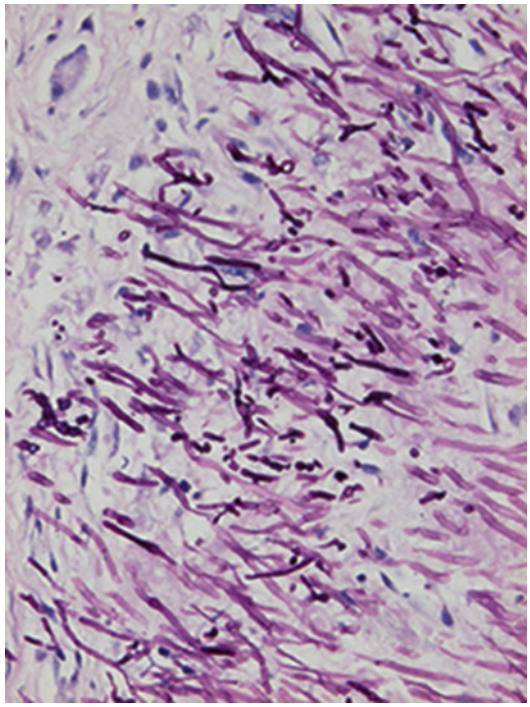

Fig. 22 Candida (original magnification x200, H&E): Candidal yeast forms in small bowel allograft

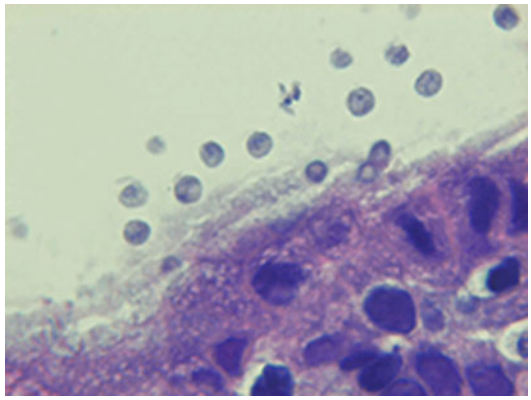

Fig. 23 Cryptosporidium (original magnification x400, H&E): Cryptosporidial organisms along mucosa of small bowel allograft

Bacterial overgrowth in bowel allografts (as compared to the density of the normal flora) can be evident in biopsies and the pathologist should communicate this information. Among potentially important bacterial infections in bowel allografts are atypical mycobacteria that can cause

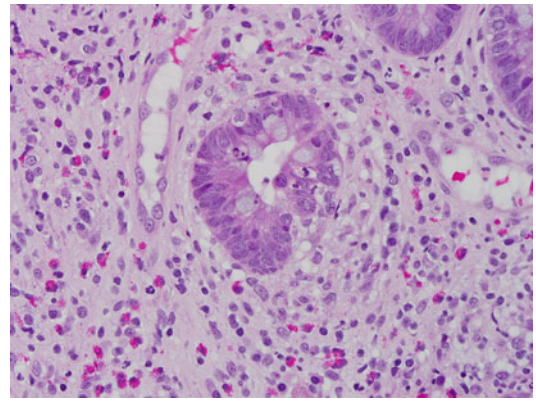

Fig. 24 Inflammatory Bowel Disease (IBD) in allograft (original magnification x400, H&E): Secondary IBD-like changes in long-term bowel allograft showing high magnification of acute colitis component, with neutrophils infiltrating crypt and surrounding mixed inflammatory cell infiltrate.

significant graft dysfunction. There are also several fungal and parasitic pathogens, including Candida (Fig. 22) and cryptosporidium (Delis et al. 2002) (Fig. 23) that are in the GI tract and which can involve the allograft.

Recurrent Disease and Other Entities

The reappearance of original systemic or intestinal disease in the bowel allograft of ITx or MVTx patients is not as frequent a complication as with other solid organ allografts (e.g., liver, kidney). Patients with inflammatory bowel disease (IBD) (e.g., Crohn's) receiving bowel allografts may show re-involvement in the transplant (Sustento-Reodica et al. 1997). There may also be secondary IBD involvement of GI allografts (Fig. 24) with certain systemic diseases such as Primary Sclerosing Cholangitis. MVTx patients that originally had intra-abdominal neoplastic disorders (e.g., desmoid tumors) (Moon et al. 2005) may display tumor recurrence after transplantation within intra-abdominal or extraperitoneal space.

A common complication in GI transplants is the manifestation of inflammatory lesions and processes that have an ambiguous or unexplained origin. For example, in some ITx and MVTx patients, there is the development later in the

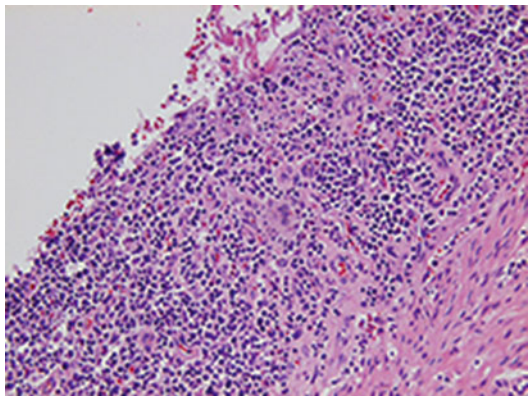

Fig. 25 Intestinal ulcers (original magnification x100 H&E): Persistent ulcer in small bowel allograft with prominent plasmacytic component. The lesion had a high EBV viral load from the paraffin block but was negative for antigen receptor gene rearrangement studies

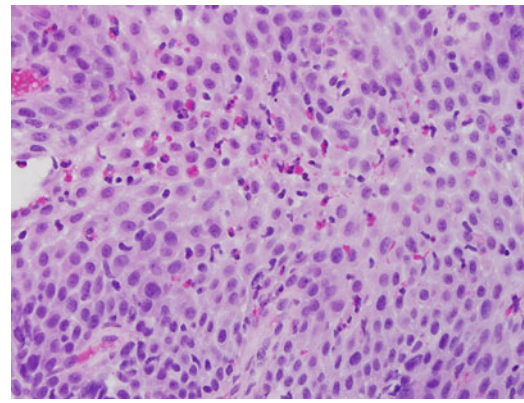

Fig. 26 Eosinophilic colitis (original magnification x400, H&E): Prominent and persistent chronic colitis (and enteritis) was present in the allografts of this multivisceral transplant patient with a very high proportion of eosinophils. The patient demonstrated increased allergic symptoms

posttransplant course of persistent ulcers that can involve graft, native GI tissue, or both (Sarkar et al. 2006). These ulcers (Fig. 25) can originate from several causes, including EBV+ PTLD (the most common cause), smoldering acute rejection, infections, and some cases that remain of undetermined etiology.

Among other nonalloimmune miscellaneous inflammatory conditions that can affect the small intestinal allograft and native small intestine (Martland and Shepherd 2007) is active enteritis of undetermined etiology. This entity displays acute inflammation in lamina propria and/or surface epithelium with focal ulceration and crypt abscesses, occurring on a background of chronic inflammation. Several potential pathogenic mechanisms of this entity include stasis, altered bacterial flora, ischemia, prolapse, and mucolysis. Some NOD2 gene polymorphisms are associated with altered bacterial clearance and increased inflammatory infiltrate (Fishbein et al. 2008).

It is not unusual for allograft and native gastrointestinal and colonic mucosa to demonstrate consistent infiltration with eosinophils (Rothenberg 2004). Although there have been some associations with allergy, the exact pathophysiology often remains unknown. There may also be an association with malabsorption, protein losing enteropathy, persistent acute rejection, and refractory ulcers. The eosinophilic infiltration can extend from the esophagus (e.g., eosinophilic esophagitis) throughout the entire GI tract (Fig. 26) and hyperplastic polyps may form. Some inflammatory lesions have a high vascular component (e.g., hemangioma-like) with erosion and mucopurulent material, resembling a pyogenic granuloma of the skin (Carmen Gonzalez-Vela et al. 2005).

Classical regenerative changes can transpire due to healing after acute rejection, infectious enteritis, or after ischemic injury.

Graft-versus-Host Disease (GVHD) can occur in skin, native alimentary tract, and other systems of ITx or MVTx patients (Zhang and Ruiz 2010). The histopathological features of GVHD in native GI tissue can resemble acute cellular rejection with increased crypt epithelial cell apoptosis and inflammatory infiltrate (Fig. 27); thus, the clinical history and origin of the tissue sample (whether from allograft or native) is critical to know in order to diagnose GVHD.

Compared to other solid organ allografts, there is a high incidence of Post-Transplant Lymphoproliferative Disease (PTLD) in ITx and MVTx patients due to the prolonged immunosuppression (Ruiz et al. 2004b). This common and serious complication escalates in frequency with extended

duration of the time posttransplant and often does exhibit involvement of the allograft. While EBV infection is frequently associated with PTLD, EBV-negative PTLD can also be present. The described histopathological progression of PTLD in the bowel includes an evolution from plasmacytic hyperplasia (an early lesion), polymorphic PTLD, monomorphic PTLD, and frank lymphoma (Table 2) (Vardiman et al. 2009). The observation of lymphoplasmacytic infiltrates (i.e., plasmacytic hyperplasia), a suspected precursor lesion of PTLD, is common in bowel allograft biopsies as the time from transplant extends and epithelial structures may be effaced by the infiltrate (Fig. 28). EBV staining by EBER (Fig. 29) and immunostaining for the presence and relative composition of B and T cells within the infiltrate is useful in evaluating possible PTLD (Parker, Bowles et al. 2010). Antigen receptor gene rearrangement studies for T- and B-cell antigen receptors from the paraffin block can also be worthwhile for an assessment of potential monoclonality. Monomorphic PTLDs can be of T- or B-cell origin and are recognized as neoplastic. PTLD lymphomas are classified according to their architectural and cytological features in a fashion identical to lymphomas occurring in native tissue (Parker, Bowles et al. 2010).

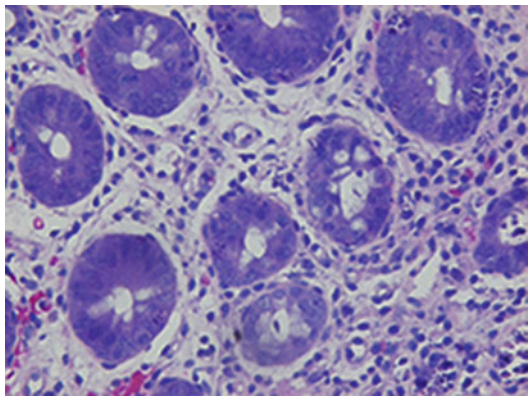

Fig. 27 GVHD in native colon of patient with small intestinal allograft (original magnification x400, 55a, H&E). High magnification of colonic epithelium showing significant apoptosis of the glandular lining cells

Conclusion

Small intestinal transplantation has developed into a viable treatment option for patients with gastrointestinal failure and potential life-threatening complications due to parenteral nutrition. The surgical outcome as well as short-term patient and graft survival has improved dramatically over the past several decades. In part, this improvement is related to an advancement of surgical techniques, superior and more selective immunosuppressive

Table 2 Morphologic categories of PTLD

"Early" lesions. Plasmacytic hyperplasia (PH) and infectious mononucleosis-like PTLD	Lymphoid proliferations that differ from typical reactive hyperplasia in having a diffuse proliferation of plasma cells and immunoblasts, but do not completely efface the architecture of the tissue
Polymorphic PTLD	Destructive lesions composed of immunoblasts, plasma cells, and intermediate sized lymphoid cells that efface the architecture of lymph nodes or form destructive extranodal masses
Monomorphic PTLD	Monomorphic B-cell PTLD: Sufficient architectural and cytologic atypia to be diagnosed as lymphoma on morphologic grounds, and expression of B-cell antigens. Nodal architectural effacement and/or invasive tumoral growth in extranodal sites with confluent sheets of transformed cells Monomorphic T-cell PTLD: Sufficient atypia and monomorphism to be recognized as neoplastic and should be classified according to the classification of T-cell neoplasms
Hodgkin's Lymphoma and Hodgkin's lymphoma-like PTLD	Since Reed-Sternberg-like cells may be seen in polymorphic PTLD, the diagnosis of Hodgkin's Lymphoma should be based on both classical morphologic and immunophenotypic features

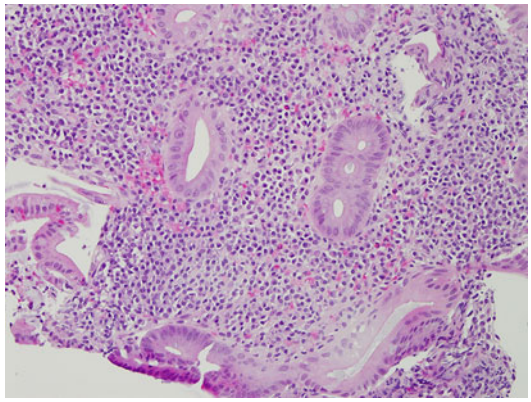

Fig. 28 Posttransplant Lymphoproliferative Disease (PTLD) (original magnification x200, H&E). Expansile mild lymphoplasmacytic infiltrate present with inflammatory infiltrate mainly consisting of lymphoplasmacytic population along with minor eosinophil component. There was minimal epithelial injury

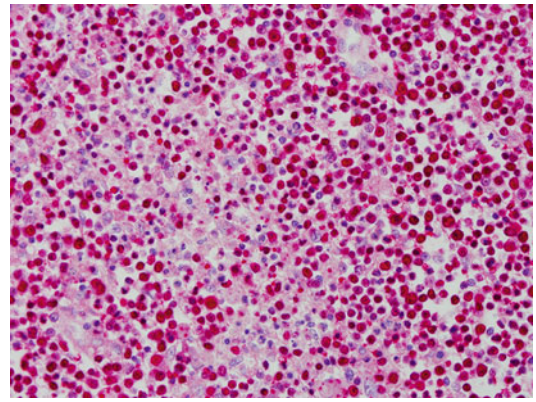

Fig. 29 Posttransplant Lymphoproliferative Disease (PTLD) (original magnification x200, EBV ISH): In situ hybridization for EBV shows extensive number of positive cells in B cell lymphoma that developed in intestinal transplant patient

agents, and a better conception and identification of the pathologic complications after transplantation. Acute rejection, chronic rejection, infectious enteritis, and PTLD remain as serious complications that typically require histopathological evaluation of graft biopsies. Transplant pathologists are obligated to understand and incorporate the clinical information and the pathophysiologic mechanisms of graft injury, with the morphological changes of tissue samples in order to generate the most specific diagnosis to the treating physicians. Ultimately, this "complete" appraisal of the GI transplant biopsies helps yield a realistic assessment of the probable clinical outcome.

Cross-References

► Viral Infections After Intestinal Transplantation

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Viral Infections After Intestinal Transplantation

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Abstract

Intestinal transplantation is a life-saving alternative for patients with intestinal failure, slow growing tumors, or other varied disorders. The complexity of the transplant, along with the use of intense immunosuppression to prevent rejection, and a unique microbiome interaction within the allograft, places these patients at high risk for common as well as opportunistic infections. Viral infections pose a significant challenge for intestinal transplant recipients. Common respiratory infections including influenza, respiratory syncytial virus, or parainfluenza can cause significant morbidity and may last for longer time compared to immunocompetent hosts. Both cytomegalovirus and adenovirus may cause a systemic disease along with viral enteritis. Epstein-Barr virus-related posttransplant lymphoproliferative disorder may be present along the intestine, alternating areas of normal mucosa or rejection. Enteric viruses usually cause protracted diarrhea and may be hard to differentiate from episodes of rejection. Moreover, intestinal transplant recipients may eliminate (shed) these viruses for several weeks to months. Management of these infections is usually challenging due to the lower age of the recipients. A reduction of immunosuppression and a high index of suspicion is necessary to balance management of infections and graft function. Treatment is usually extrapolated from other transplants, but the drug armamentarium remains limited.

Keywords

Intestinal transplantation · Opportunistic infections · Cytomegalovirus · Herpes viruses · Infectious diarrhea · Respiratory tract infections

Introduction

Intestinal transplantation has become a life-saving option for patients with intestinal failure, complications of parenteral nutrition and central venous access, benign or slow growing mesenteric tumors, congenital mucosal disorders, and complete splanchnic venous thrombosis (Rege and Sudan 2016). Although intestinal transplantation restores organ function to a certain degree, it is associated with significant infectious complications.

The increased risk of infections is multifactorial: high immunogenicity of the allograft, intense immunosuppression, ischemia-reperfusion injury that increases the risk of bacterial translocation across damaged intestinal mucosa, presence of significant amount of microorganisms in the allograft, and alteration of the allograft microbiome (Oh et al. 2012; Rege and Sudan 2016). More data on epidemiology and management of viral infections in IT have been published over the last several years, although many times the management of these infections is based on data extrapolated from other allograft recipients. Viral enteritis of the allograft poses a particular challenge, due to the difficulty in differentiating infection from rejection that would trigger adjustment of immunosuppression. Even more, viral enteritis can be associated with changes in the absorption of the immunosuppressive drugs (Adeyi et al. 2010; Fruhwirth et al. 2001; Roos-Weil et al. 2011). Commonly implicated viruses include herpes virus family (especially cytomegalovirus, Epstein-Barr virus), adenovirus, norovirus, rotavirus, and influenza virus.

Herpes Viruses

Cytomegalovirus (CMV)

Epidemiology. Risk factors. CMV infection continues to have a significant impact after IT, being the most commonly diagnosed viral infection despite improvements in prevention strategies (Abu-Elmagd et al. 2009a), with an incidence between 16% and 40% (Abu-Elmagd et al. 2009a; Bueno et al. 1997; Florescu et al. 2012; Ambrose et al. 2016; Timpone et al. 2016), and a relapse rate as high as 86% (Florescu et al. 2012) and immunomodulatory effect that might trigger allograft rejection, reactivation of other latent viruses, favor progression to posttransplant lymphoproliferative disorder (PTLD), and development of bacterial and fungal infections (Rubin 2007; Freeman 2009; Razonable et al. 2013).

The risk of CMV infection depends on several factors: (1) the donor and recipients CMV serologic status, with the highest incidence and more severe disease CMV D+/R− recipients (Florescu et al. 2012; Ambrose et al. 2016; Razonable et al. 2013); (2) the allograft type; (3) the overall degree of immunosuppression, with a higher risk of CMV infections reported with induction therapy with lymphocyte depleting antibodies compared with interleukin-2ra (Kalil et al. 2009; Razonable et al. 2013) and with treatment for rejection (steroids or polyclonal antibodies) (Razonable et al. 2013); the use of mTOR has been associated with lower risk for CMV disease (Ghassemieh et al. 2013; Kobashigawa et al. 2013), (4) HHV-6 and HHV-7 reactivation, due to their immunomodulatory effects, and (5) pro-inflammatory state induced by bacterial and fungal infections (Adams et al. 2002; Florescu et al. 2013b). Several other factors have been recently described as potential risk factors, especially in high risk transplant recipients: long cold ischemia time, male gender, and combined transplant with kidney and renal dysfunction (Nagai et al. 2016). In contrast, D−/R− sero-status and higher doses of CMV immunoglobulins might have protective effect, although efficacy of CMV immunoglobulin administration is still debatable (Nagai et al. 2016). The high burden of the disease in this population can be explained by several factors: unpredictable absorption of valganciclovir in patient with rapid transit, decreased conversion of prodrug valganciclovir to ganciclovir due to deficiency of esterase activity (hepatic and enteric dysfunction after transplantation, competition with other drugs for the same substrate), and difficulty adjusting the dose of ganciclovir or valganciclovir in patients with renal insufficiency (Florescu et al. 2012; Jain et al. 2005; Silva et al. 2016).

Clinical presentation. The time to first CMV infection ranges 1–80.4 weeks (Ambrose et al. 2016; Timpone et al. 2016); CMV seropositive recipients tend to reactivate the disease earlier (1–35.9 weeks) than patient with primary CMV infection (range 7.1–80.4 weeks) (Ambrose et al. 2016). CMV disease was diagnosed earlier in patients who developed enteritis compared with all other forms of CMV disease (Florescu et al. 2012). Patients with CMV disease seem to be more likely to be infected with resistant CMV strain (Timpone et al. 2016). Patients can present with CMV viremia prior to development of CMV disease, or viremia never develop, even with tissue invasive disease (Avsar et al. 2014; Humar et al. 1999). Gastrointestinal tract involvement, from the oral cavity to the anal area, is commonly described; the patients present with nausea, vomiting, abdominal pain, and watery or bloody diarrhea. Graft involvement has been frequently described in IT (Florescu et al. 2012; Manez et al. 1995; Ambrose et al. 2016; Silva et al. 2016) and it is possible that the allograft has a large number of donor leukocytes with latent CMV; also most likely there is an aberrant immune response within the allograft manifested as local graft-versus-host reaction and host-versus-graft reaction (Iwaki et al. 1991; Paya 2003; Roche et al. 1981). CMV pneumonitis, although not common, is one of the most severe complications; patients present with fever, shortness of breath, and nonproductive cough (Florescu and Kalil 2011; Florescu et al. 2012).

CNS disease is a rare complication in SOT and it has been reported to occur more than 4 months after transplantation (Florescu and Kalil 2011).

Diagnosis. CMV culture is not practical for clinical purposes since the virus grows slowly and isolation of the virus does not necessarily reflect active disease (e.g., sputum). CMV-specific antibodies (igM and IgG) are useful to determine the immune status of the recipient, but have no role in posttransplant management (Humar and Snydman 2009). CMV pp65 antigen is a semiquantitative test, sensitive and specific, which has been used to initiate preemptive therapy, to diagnose CMV infection and to assess response to treatment (Kotton 2013). The test has several limitations: it is not standardized, requires more blood than a PCR assay (less desirable in pediatric population), requires immediate processing of the samples, and is labor-intensive requiring technical skills for reading of the assay, and leukopenia decreases its sensitivity (Lugert et al. 2009; Kotton 2013). Real-time polymerase chain reaction (PCR) is becoming the preferred test since it is faster, less labor intensive, more sensitive and specific, can detect CMV infection earlier, and can be used for preemptive strategies and to assess response to antivirals (Lugert et al. 2009; Gimeno et al. 2008; Meyer-Koenig et al. 2006; Sanghavi et al. 2008; Tanaka et al. 2000; Kotton 2013; Razonable and Hayden 2013). There is significant variability of CMV PCR testing and performance among individual laboratories make difficult meaningful inter-institutional comparison of patient results (Pang et al. 2009). To address these issues, a new international standard was approved by World Health Organization and it should be used by manufacturers and individual laboratories to calibrate individual assays for CMV (Kraft et al. 2012). For definite diagnosis of CMV tissue-invasive disease, histology examination, especially immunohistochemical techniques with monoclonal antibodies against CMV antigens and in situ hybridization remain the gold standard (Jiwa et al. 1989; Naoumov et al. 1988; Kotton 2013; Razonable et al. 2013). In small bowel biopsies, CMV inclusions can be easily seen on H&E sections (Koo et al. 2016).

Prevention of CMV infections. The standard of care for CMV prevention in most transplant programs is CMV prophylaxis or hybrid strategy regardless of CMV sero-status (Florescu et al. 2014a). The regimens used for prophylaxis depend on CMV donor-recipient mismatch and the ability to absorb oral medications. Breakthrough CMV during the first 6 months after intestinal transplantation has been reported, more commonly in the pediatric population (Avsar et al. 2014; Florescu et al. 2012; Nagai et al. 2016; Silva et al. 2016). Valganciclovir prophylaxis for 3–6 months posttransplantation is the preferred regimen for D+/R− and R+ IT recipients (Humar and Snydman 2009). Intravenous ganciclovir is used in IT patients in the immediate posttransplant period when enteric absorption is unpredictable. It is unclear if administration of CMV immunoglobulins has a beneficial impact on overall survival, but potentially prevents CMV disease and CMV-associated death (Bonaros et al. 2008). Several assays measuring CMV-specific cell-mediated immunity have been developed as potential tools in the management of CMV prevention after transplantation (Melendez and Razonable 2014). Measures of CMV-specific T-cell function could personalize the approach to the initiation/discontinuation of antiviral prophylaxis or preemptive therapy by determining when patients recovered or developed CMV-specific T-cell immune response (Melendez and Razonable 2014). As a principle, recipients with CMV-specific T-cell response below the threshold are at risk of CMV reactivation and less more likely to develop clinical and virological relapse; in contrast, recipients with CMV-specific T-cell response above a certain threshold might spontaneously clear the CMV infection and are less likely to relapse (Melendez and Razonable 2014). However, these tests are not considered standard of care at this point and no data have been published in intestinal transplant recipients.

Treatment of CMV infections. The management of CMV infections consists in reduction of immunosuppression, if possible, in combination with antiviral therapy. Ganciclovir or its prodrug

valganciclovir are considered the first-line antiviral therapy, while foscarnet, cidofovir, and leflunomide are reserved for treatment of ganciclovir-resistant CMV infection (Florescu and Kalil 2011; Kotton 2013; Razonable et al. 2013). The clinical resolution of symptoms, site of infection, and the virologic response would guide the length of therapy (Florescu and Kalil 2011; Humar and Snydman 2009). CMV viremia prompts treatment, although the threshold at which the treatment should be started remains to be determined. The therapy for viremia usually is shorter than for end-organ disease, until resolution of viremia (Razonable et al. 2013). Viral load on treatment should be monitored weekly (Humar and Snydman 2009; Kotton 2013; Razonable et al. 2013). Recipients with gastrointestinal disease since regeneration of the epithelium might take several weeks and should be treated until clinical resolution of the symptoms and virologic clearance for two consecutive weeks (Kaplan et al. 1989; Mayoral et al. 1991; Kotton 2013; Razonable et al. 2013). Valganciclovir is not ideal in patients with vomiting and diarrhea, and treatment with intravenous ganciclovir should be considered in these patients; when symptoms resolve, patients can be switch to oral valganciclovir. Although not supported by clinical trials, ganciclovir in combination with intravenous immunoglobulins is administered standard practice for recipients with CMV pneumonia (Humar and Snydman 2009; Emanuel et al. 1988; Ljungman et al. 1992; Reed et al. 1988; Schmidt et al. 1988). Intravenous immunoglobulin might be beneficial in IT patients with hypo-gammaglobulinemia (Robertson et al. 2009; Florescu et al. 2014b; Poole et al. 2016). The incidence of ganciclovir-resistant CMV has been considered to be relatively low. However, more recent studies, Ambrose et al. report 31.3–31.6% rate of resistance, most of the patients having CMV D+/R− sero-status (Ambrose et al. 2016; Timpone et al. 2016). Resistance to ganciclovir/valganciclovir is associated with mutations in the genes encoding for the phosphotransferase (UL97) and/or DNA polymerase (UL54) (Chou et al. 1995a; Chou et al. 1995b; Sullivan et al. 1993; Kotton 2013). Resistant CMV disease can be treated with foscarnet, or cidofovir; both drugs have significant side effects: bone marrow suppression, decline in renal function, electrolytes imbalance, and neurotoxicity, making challenging their long term administration (Reddy et al. 2007; Ambrose et al. 2016; Kotton 2013). Several new antiviral drugs with CMV activity are in development: Brincidofovir (Florescu and Keck 2014), Maribavir (Alain et al. 2013), and Letermovir (Melendez and Razonable 2015).

Epstein–Barr Virus (EBV) and Posttransplant Lymphoprolipherative Disorders (PTLD)

EBV is a gamma herpesvirus, with an estimated seroprevalence of 95% in the adult population worldwide. EBV is an important pathogen in solid organ transplant recipients and a major cause of disease (Green and Michaels 2013). EBV plays a major role in the development of PTLD with a 20-fold increased risk in seronegative recipients compared to seropositive recipients (Shroff and Rees 2004; Allen and Preiksaitis 2009; Bakker et al. 2007; Allen et al. 2013). Up to 60% of IT recipients have asymptomatic EBV viremia that will resolve in 40% of cases after lowering immunosuppression (Green et al. 2000; Pascher et al. 2004). PTLD is the most common type of neoplasm in transplanted children (Brennan et al. 2013; Ramos et al. 2013). The incidence of PTLD in IT recipients ranges from 21 to 32% (Abu-Elmagd et al. 2009a; Allen and Preiksaitis 2009; Nalesnik et al. 2000; Quintini et al. 2006; Reyes et al. 1996; Allen et al. 2013; Ramos et al. 2013), with a higher incidence in children than adults (26.8% vs. 9.3%) (Reyes et al. 1996). Children are more likely to be EBV sero-negative and to acquire the infection through a graft from a seropositive donor (Gottschalk et al. 2005; Allen et al. 2005; Allen and Preiksaitis 2009; Allen et al. 2013). PTLD is usually diagnosed within 1 year of IT, especially between 1 and 6 months (Abu-Elmagd et al. 2009a; Guaraldi et al. 2005; Lauro et al. 2005), although there seems to be a cumulative risk over a 10-year

period after transplantation (Allen et al. 2013). Most cases of early PTLD (<1 year after transplantation) are of recipient origin, regardless of the localization at the time of presentation (Chadburn et al. 1995; Weissmann et al. 1995), with >90% showing the EBV genome (Allen et al. 2013). PTLD may not be related to EBV and can resemble non-Hodgkin's lymphoma (Bakker and van Imhoff 2007; Faye and Vilmer 2005; Ghobrial et al. 2005).

Classic risk factors for development of PTLD include primary EBV infection, young recipient age, type of organ transplanted (intestinal transplants are at highest risk), high doses and repeated courses of lytic immunosuppressive therapy such as thymoglobulin (Allen and Preiksaitis 2009; Opelz and Dohler 2004; Quintini et al. 2006; Allen et al. 2013; Nassif et al. 2013), as well as the type and intensity of maintenance immunosuppression (Allen and Preiksaitis 2009; Bakker et al. 2007; Faye and Vilmer 2005; Opelz and Dohler 2004; Allen et al. 2013). On the other hand, induction with IL-2 receptor monoclonal antibodies or Alemtuzumab have been associated with increased risk (Allen et al. 2013; Ramos et al. 2013), while cyclosporine and tacrolimus were associated with increased risk of PTLD (Bakker et al. 2007; Faye and Vilmer 2005), mycophenolate mofetil (Everly et al. 2007), and especially sirolimus and everolimus and have been found to reduce the risk by inhibiting cell-signaling pathways in EBV-activated lymphoid cells (Bakker et al. 2007; Preiksaitis and Cockfield 2010). It has been debated whether CMV serostatus mismatch or development of CMV disease increase the risk of PTLD (Abu-Elmagd et al. 2009a; Allen and Preiksaitis 2009; Bakker et al. 2007; Preiksaitis and Cockfield 2010; Faye and Vilmer 2005; Allen et al. 2013).

It is important to note that compared to other organ recipients, IT allograft-recipients may have concurrent episodes of PTLD and rejection, and sometimes both present in different sites of the transplanted organ (Allen and Preiksaitis 2009; Faye and Vilmer 2005; Green and Michaels 2013; Paya et al. 1999; Preiksaitis and Cockfield 2010; Allen et al. 2013). This special population is also at an increased risk of PTLD despite prior EBV seropositivity. Compared to EBV-seropositive IT recipients, seronegative IT recipients who acquire primary EBV infection are at higher risk of PTLD (Allen and Preiksaitis 2009; Faye and Vilmer 2005; Green and Michaels 2013; Mazariegos 2009; Paya et al. 1999; Allen et al. 2013). Moreover, EBV-seropositive IT recipients are at greater risk of acquiring PTLD when compared to other organ recipients such as liver, kidney, or heart (Green and Michaels 2013; Mazariegos 2009).

PTLD encompasses a wide spectrum of disease manifestations that range from polyclonal proliferation of B-lymphocytes resembling infectious mononucleosis, polymorphic proliferation of B cells, monomorphic proliferation of cells resembling non-Hodgkin lymphomas, and Hodgkin's disease (Bakker and van Imhoff 2007; Bakker et al. 2007; Baldanti et al. 2000; Faye and Vilmer 2005; Paya et al. 1999; Allen et al. 2013). More than 80% of PTLD involves B-lymphocytes, but T-cell PTLD may be found in up to 15% of the cases (Bakker et al. 2007; Faye and Vilmer 2005).

Clinical manifestations can be divided in those related to the virus itself, manifesting as infectious mononucleosis with fever, malaise, lymphadenopathy and exudative tonsillitis, abdominal pain, organomegaly, and diarrhea (Bakker and van Imhoff 2007; Faye and Vilmer 2005; Green et al. 1999b; Paya et al. 1999; Weintraub et al. 2014). Other important manifestations may include hepatitis, pneumonitis and even hematological syndromes with leukopenia, thrombocytopenia, or hemophagocytic syndrome (Allen et al. 2013). A thorough clinical exam may be helpful as up to 50% of the cases may present with lymph node involvement (Faye and Vilmer 2005; Bakker et al. 2007; Nalesnik et al. 2000; Allen et al. 2013). Extranodal disease is common, involving the gastrointestinal tract more commonly, followed by the liver, kidney, sinuses, bone marrow, or lungs. A high percentage of cases may involve the transplanted organ, possibly because of a more tolerant microenvironment on the graft (Bakker and van Imhoff 2007). In a large series, the intestinal allograft was involved in 71% of cases (Abu-Elmagd et al. 2009b).

Laboratory clues include atypical lymphocytosis, anemia, leukopenia, abnormal liver function tests, or elevated lactate dehydrogenase (Bakker and van Imhoff 2007; Faye and Vilmer 2005; Green et al. 1999a; Paya et al. 1999). Use of serologic tests has no value.

Imaging studies such as computed tomography (CT) scans or magnetic resonance imaging (MRI) may play a role in identifying suspicious lesions or to identify tissues that warrant biopsies for histopathologic evaluation (Allen et al. 2013; Nijland et al. 2016).

Histopathology of biopsied tissues or masses is the cornerstone for diagnosis and this can be enhanced with the use of EBV-encoded RNA (EBER) probe, as well as immunophenotypic determination with anti-CD 20 staining (Allen et al. 2013; Nijland et al. 2016). Early post-transplant, as well as serial EBV viral load monitoring, is a common practice and finding elevated EBV viremia may increase the suspicion for later development of PTLD, but it lacks specificity as it may also be elevated in asymptomatic patients (Allen et al. 2001; Allen and Preiksaitis 2009; Allen et al. 2013; Nijland et al. 2016). The cutoff at which a patient should be worked up for PTLD is also debatable and should always be correlated back with the patient's symptomatology (Allen and Preiksaitis 2009; Bakker et al. 2007; Faye and Vilmer 2005; Green et al. 1999a; Allen et al. 2013; San-Juan et al. 2015). A recent study found that peak EBV viremia greater than 1000 copies/10^5 lymphocytes was associated with higher risk for PTLD (Weintraub et al. 2014); however, at lower viral load counts specificity is lower, thus including patients without PTLD (Fellner et al. 2016). Persistently elevated viral load in asymptomatic patients may be a useful tool to guide a reduction in immunosuppression whenever possible (Allen and Preiksaitis 2009; Baldanti et al. 2000; Allen et al. 2013; Ramos et al. 2013; San-Juan et al. 2015). Serially negative EBV viral load measurements over the first 6 months after transplantation may have negative predictive value for early PTLD (Green et al. 2000) but may miss late onset and EBV-negative disease (Allen and Preiksaitis 2009; Bakker et al. 2007; Allen et al. 2013). A recent retrospective chart review of 81 pediatric small bowel transplant recipients found that those who developed PTLD had higher EBV viral loads before diagnosis, but viral load had decreased at time of PTLD diagnosis, thus suggesting that relying on viral load to determine risk or likelihood of PTLD may not be the best approach (Nassif et al. 2013). Unfortunately, performance of viral load assays for EBV lacks uniformity between laboratories. Preiksaitis et al. evaluated the performance of EBV viral load testing among 28 laboratories in the United States, Canada, and Europe using clinical samples and cell line diluted in plasma samples and found a significant interlaboratory variability, with only 47% of results falling within acceptable standards of variation (Preiksaitis et al. 2009).

Prevention of PTLD would be ideal by identifying high-risk patients prior to transplantation and monitoring them closely. There are limited data to support antiviral prophylaxis with acyclovir or ganciclovir (Darenkov et al. 1997; Davis et al. 1995; Funch et al. 2005), although a recently published systematic review found no beneficial effect of antiviral prophylaxis for the prevention of PTLD, even in high-risk naïve patients and across all organ types (AlDabbagh et al. 2016). Antiviral agents are only active against the lytic phase of EBV; they may reduce recruitment of peripheral lymphocytes and development of latently infected cells (Allen 2013). It may be hypothesized that inhibiting lytic EBV replication may prevent further B cell infection and decrease the growth of the latently infected B cell population (San-Juan et al. 2015). Based on currently available data, a recommendation to use antiviral prophylaxis cannot be made at this time (Allen and Preiksaitis 2009; Humar et al. 2006; Allen et al. 2013).

Treatment of PTLD should always begin with reduction of immunosuppression (Allen et al. 2013; Nijland et al. 2016), in order to restore cytotoxic T lympholyte (CTLs) function (Wistinghausen et al. 2013), and will result in clinical remission in up to 50% of early PTLD cases (Faye and Vilmer 2005; Allen and Preiksaitis 2009; Allen et al. 2013). This approach may not always be feasible, especially early after transplantation or when PTLD may occur

concomitantly with an episode of rejection (Green et al. 1999b; Paya et al. 1999; Allen and Preiksaitis 2009; Faye and Vilmer 2005; Allen et al. 2013). Surgical management is usually needed for local complications (perforations or bleeding). (Preiksaitis and Cockfield 2010). Rituximab, a monoclonal antibody against CD20, is used when reduction of immunosuppression is not sufficient. Response rates to rituximab may be as high as 78% with remission rates up to 53% especially if more than one course of therapy is employed (Choquet et al. 2006; Gonzalez-Barca et al. 2007; Oertel et al. 2005). Despite the growing body of evidence on rituximab effectiveness and its widespread use, potential long term toxicities are not well known. More studies are needed before rituximab can be established as a proven second-line therapy (Green and Michaels 2013).

Modified cytotoxic chemotherapy can be tried in those cases that fail to respond after reduced immunosuppression and rituximab, but relapse rates as high as 20% have been observed (Gross et al. 2005). The use of low dose chemotherapy, when feasible, has the advantage of preserving some EBV-related cytotoxic T-cell function, in order to control proliferation of EBV infected B cells (Wistinghausen et al. 2013). The use of rituximab, especially with lower intensity chemotherapy regimens, has shown promising results in clinical trials. (Dharnidharka and Gupta 2010; Elstrom et al. 2006; Gross et al. 2012). More aggressive or conventional chemotherapy can achieve response rates between 74% and 100% when combined with rituximab (Lee et al. 2007), but it is reserved for some adults with PTLD and as the ultimate resort for children with refractory monomorphic, late onset, EBV-negative, Hodgkin-like, or T-Cell PTLD (Allen et al. 2013; Wistinghausen et al. 2013).

Newer approaches such as adoptive immunotherapy have emerged in recent years and may prove useful to the armamentarium to manage PTLD (Bollard 2013; Nourse et al. 2011; San-Juan et al. 2015; Wistinghausen et al. 2013). Experience comes from the hematopoietic stem cell transplant (HSCT) population, where response rates are above 70% with this treatment alone. There are several challenges may preclude its use in SOT recipients. Donor cytotoxic T lymphocytes are not readily available and most PTLD cases arise from the donor, thus efficacy would be limited. Autologous CTLs have been successfully used in SOT recipients with PTLD, although experience is limited to case reports and case series. Its use may also be challenged by the need of ongoing immunosuppression and delays in manufacturing CTLs (Petrara et al. 2015; Wistinghausen et al. 2013), although there are now mouse models with CTLs resistant to calcineurin inhibitors (Nijland et al. 2016). Using stored HLA-typed EBV-specific CTLs could prove the best alternative, as these cells would be readily available for use, and results show variable response rates without an increase in toxicity or rejection episodes (Haque et al. 2007; San-Juan et al. 2015). There is currently no available vaccine to prevent PTLD in SOT recipients. A recombinant EBV vaccine trial showed effect on EBV infection, but saw a 78% reduction of symptomatic infectious mononucleosis (Sokal et al. 2007). It is still unclear on which protein should be used as target for the vaccine, clinical trials may not be easy to carry out as timing for vaccination is not well known, and development of PTLD may take several years (Nijland et al. 2016).

Prognosis of PTLD depends on the type of tumor (pleomorphic vs. other types such as monomorphic disease) and disease localization. Factors that predict poor outcomes include older age, poor performance status, multisite disease, CNS involvement, EBV-negative or T-cell PTLD, and monoclonal disease (Allen 2013). Prognosis is best for patients with localized disease of the graft or gastrointestinal tract (Preiksaitis and Cockfield 2010). It has been reported that mortality from early PTLD can be as high as high as 50% (Reyes et al. 1996); however, the introduction of newer immunosuppressive regimens has resulted in dramatic improvements in survival rates, which can be as high as 92% at 1 year and 75% at 5 years (Abu-Elmagd et al. 2009b).

Herpes Simplex Virus (HSV)

Primary infection caused by HSV-1 usually occurs during childhood (Tunback et al. 2007) with a seroprevalence of 44% by age by age 19, on the other hand, prevalence of HSV-2 is uncommon in the pediatric population, with sero-prevalence of 1.6% in the 12- to 19-year-old age group (Xu et al. 2006). Prevalence of both HSV-1 and HSV-2 in the adult transplant population infection occurs either through close contacts (Tunback et al. 2007) or from the graft (Miller and Dummer 2007). The highest risk for viral reactivation is between weeks 2 and 3 post-transplant (Wilck et al. 2013). Risk for reactivation in IT recipients is similar to other graft recipients; however, primary infection is of great concern after the period where antiviral prophylaxis is given, primarily for those who are below 2 years of age.

Common clinical manifestations include blisters or ulcerative lesions in oro-labial, genital, or perianal regions, while more severe manifestations may include hepatitis, pneumonitis, encephalitis, or disseminated visceral disease (Miller and Dummer 2007; Razonable 2011; Zuckerman and Wald 2009). Gastrointestinal involvement usually presents with esophagitis (Zuckerman and Wald 2009; Wilck et al. 2013); colitis is rare (Delis et al. 2001) and involvement of the graft has not been described. Disseminated disease may present with fever, leukopenia, and hepatitis (Wilck et al. 2013).

Risk for HSV may be determined pretransplant with specific HSV IgG. Those who are seronegative are at risk of donor derived or primary infection, while those who are seropositive are at risk for viral reactivation posttransplant (Wilck et al. 2013). Classically, OKT3 and mycophenolate use have been associated with higher reactivation risk, but there are no data available, to stratify risk based on different immunosuppressive drugs or regimens (Wilck et al. 2013).

Diagnosis of HSV may be established on clinical grounds, especially for orolabial or genital lesions. Viral culture may be used for diagnostic confirmation, although its use to guide therapeutic decisions is limited as turnaround time is usually 5 days (Wilck et al. 2013).

DFA testing is quite useful to quickly diagnose HSV in skin or mucosa (genital, oral, or orolabial lesions) and or broncho-alveolar lavage (BAL) specimens, providing answers within a few hours (Wilck et al. 2013). Detection of HSV-DNA by PCR may be necessary to increase the diagnostic yield either in blood, cerebrospinal fluid, or biopsy samples, is helpful when disseminated disease or end organ involvement is suspected, and has become the procedure of choice (Razonable 2011; Zuckerman and Wald 2009; Wilck et al. 2013). HSV detection by PCR is especially useful when meningitis or encephalitis is suspected (Wilck et al. 2013). Antibody testing is not useful to detect viral reactivation; histopathology and tissue immunohistochemistry are used when organ involvement is present, especially in cases where viral contamination from blood or body fluids may be present (Wilck et al. 2013).

All antiviral regimens used to prevent CMV reactivation also prevent HSV reactivation, and the recommended duration of prophylaxis for HSV only is 4 weeks (Wilck et al. 2013; Zuckerman and Limaye 2013). However, almost all recipients end up prophylaxis for CMV for 3–6 months regardless of HSV serostatus (Zuckerman and Limaye 2013).

Oral antiviral drugs such as acyclovir, famciclovir, or valacyclovir may be sufficient for the treatment of mucocutaneous or localized disease as long as the patient has reliable intestinal absorption (e.g., adequate tacrolimus levels). Intravenous acyclovir may be used in patients with extensive mucocutaneous or skin disease, disseminated disease or organ involvement, CNS disease, or those with impaired intestinal absorption (Wilck et al. 2013; Zuckerman and Limaye 2013). It should be noted that intravenous acyclovir dosing ranges between 5 and 10 mg/Kg every 8 h, but it should be noted that children metabolize acyclovir more rapidly and higher doses up to 20 mg/Kg every 8 h are necessary (Wilck et al. 2013). For patients with acyclovir resistance, reduction of immunosuppression should be attempted. Treatment of resistant HSV with antiviral drugs includes forscarnet or cidofovir, but special attention to renal function and electrolyte management are needed as both drugs have

nephrotoxicity potential and need to be administered intravenously (Wilck et al. 2013; Zuckerman and Limaye 2013). It is important to recognize the disease early and begin antiviral therapy promptly, since mortality for untreated disseminated disease can be as high as 80% (Wilck et al. 2013; Zuckerman and Limaye 2013).

Varicella-Zoster Virus (VZV)

VZV is an alpha herpesvirus that is exclusive to humans and may be acquired through direct contact or airborne spread (Gnann and Whitley 2002). More than 90% of cases occur before adolescence, with the highest incidence peaking between 1 and 9 years of age (Heininger and Seward 2006). Because most children and young adult SOT recipients have been vaccinated for varicella, only a small fraction of SOT recipients are seronegative for VZV and thus susceptible to primary infection (Zuckerman and Limaye 2013). Pediatric recipients who may undergo IT before receiving VZV vaccination would have lower seroprevalence for VZV antibodies. (Lynfield et al. 1992; McGregor et al. 1989).

Infection is usually acquired via contact or inhalation, and those with preexisting antibodies seem to have some protection (Pergam et al. 2013; Zuckerman and Limaye 2013).

The most important risk factors for infection include seronegativity and the use of immunosuppression (Pergam et al. 2013). Risk factors for reactivation include age and decreased cell-mediated immunity against varicella, which may be related to the intensity of immunosuppression (Pergam et al. 2013). There are no data on risk factors for IT recipients, but information may be extrapolated from lung transplant recipients who usually receive similar degrees of immunosuppression. Primary varicella presents with a vesicular rash that spares the palms and soles accompanied by crusting of older lesions and new papular lesions that appear for several days. Highly immunosuppressed patients may suffer a more protracted course with disseminated disease and multiorgan involvement (Zuckerman and Limaye 2013). Classic clinical manifestations of zoster reactivation include a dermatomal vesicular or papular rash preceded by pain or paresthesias, but disseminated disease may be severe and indistinguishable from primary varicella (Pergam et al. 2013). Disseminated zoster can present with fever, abdominal pain, and visceral involvement including meningitis/encephalitis, hepatitis, pneumonitis, and/or pancreatitis; the characteristic skin lesions may be atypical (hemorrhagic) and take longer to appear, possibly delaying the diagnosis (Miller and Dummer 2007; Zuckerman and Limaye 2013). The median time for zoster reactivation is 9 months posttransplant (Gourishankar et al. 2004).

Diagnosis is suspected on clinical grounds with findings of classic vesicular lesions, although sometimes lesions can be atypical with hemorrhagic appearance (Zuckerman and Limaye 2013). Using direct fluorescent antibody (DFA) testing can help with rapid diagnosis when skin lesions are present. PCR to detect VZV-DNA can be used in blood, spinal fluid, vesicle fluid, or tissues and is the method of choice when disseminated disease or viremia is suspected (Pergam et al. 2013).

Therapy with intravenous acyclovir should be used for disseminated or viral disease including CNS, ophthalmic involvement, and herpes-zoster oticus. Treatment of primary chickenpox in IT recipients is also warranted because of the high risk of severe and disseminated disease. Localized disease can be treated with oral valacyclovir or famciclovir when the patient can take orally and has close follow-up (Pergam et al. 2013). Therapy should be continued until the virus is cleared and all lesions have crusted (Pergam et al. 2013).

Posttransplantation antiviral chemoprophylaxis with acyclovir is recommended for all seropositive recipients who do not receive CMV prophylaxis, for the same duration as for Herpes-simplex virus (4 weeks) (Razonable et al. 2005; Slifkin et al. 2004; Pergam et al. 2013). Long-term antiviral prophylaxis is not routinely offered (Pergam et al. 2013). Current guidelines recommend vaccination with Oka vaccine (Varivax®) at least 4 weeks before transplantation in sero-negative patients; posttransplant

vaccination is not recommended because of the risk of disseminated disease (Kraft and Shaw 2006; Danziger-Isakov et al. 2013), although it can be considered under special situations (Pergam et al. 2013). There is some evidence to support varicella vaccination in immunosuppressed patients (Hata et al. 2002; Khan et al. 2006; Levin et al. 2006; Weinberg et al. 2006). Khan et al. showed a 64% seroconversion rate after varicella vaccination in 26 pediatric liver transplant recipients with an adverse event rate similar to the general population (Khan et al. 2006). Varicella vaccination has been evaluated in pediatric liver transplant recipients with promising results, which included seroconversion in all vaccinated children and persistence of seropositive titers after more than 1 year follow-up. Side effects included frequent local and mild systemic reactions (Posfay-Barbe et al. 2012). Seronegative patients exposed to VZV should receive postexposure prophylaxis with varicella immunoglobulin (VariZIG™) within 96 h of exposure; however, limited availability may preclude its use (Pergam et al. 2013; Prelog et al. 2011). Valacyclovir is the preferred agent for antiviral prophylaxis, given low absorption rates and decreased bioavailability of acyclovir (Pergam et al. 2013; Zuckerman and Limaye 2013). If antiviral prophylaxis is used, it should be started within 7–10 days postexposure and continued for at least 7 days (Pergam et al. 2013).

Human Herpesvirus-6 and -7 (HHV-6 and HHV-7)

HHV-6 and HHV-7 affect the general population very early in life. Since >95% of the population is seropositive by 5 years of age, almost all infections in SOT recipients are caused by viral reactivation (Le et al. 2013; Razonable 2011, 2013) HHV-6 has 2 variants, HHV-6A and HHV-6B; HHV-6B causes most infections posttransplantation (Carratala et al. 2012; Florescu et al. 2013b; Le et al. 2013; Razonable 2011, 2013). HHV-6 establishes latency in mononuclear cells and viral reactivation usually occurs between 2 and 4 weeks for HHV-6 and 4 weeks for HHV-7 posttransplant (Petrisli et al. 2010). Previous sero-positivity is an important risk factor, although the highest risk for reactivation seems to be the net state of immunosuppression (Razonable 2013) and induction therapy, especially with lytic agents such as thymoglobulin. The majority of patients with HHV-6 infection are asymptomatic, but 1% may present with fever, hepatitis, bone marrow suppression, pneumonitis, or encephalitis; CMV-like syndrome has been reported, as well as a mononucleosis-like syndrome in adults (Razonable 2011; Le et al. 2013; Razonable 2013). Both HHV-6 and HHV-7 may have immunomodulatory properties, potentially increasing the risk of CMV reactivation (Kotton 2013; Razonable et al. 2013) and bacterial infections. The preferred method for diagnosis is nucleic acid detection by PCR which can also differentiate between HHV-6 and HHV-7; however, it is not possible to distinguish between acute infection or reactivation of latent infection (Le et al. 2013). Screening for HHV-6 or HHV-7 in asymptomatic patients is not currently recommended (Le et al. 2013). Diagnosis of tissue invasive disease may be helped by histopathology and usually immunohistochemistry staining of affected organs in cases of hepatitis or pneumonitis (Le et al. 2013; Razonable 2013). Most infections are asymptomatic or transient and do not warrant antiviral therapy. When treatment is indicated, it should always be accompanied by a reduction in immunosuppression since antiviral agents are not fully effective against HHV-6. Treatment is warranted for significant disease such as hepatitis, disseminated disease, and encephalitis. It may be possible to achieve therapeutic concentrations of antiviral agents against HHV-6; however, HHV-7 can be resistant to ganciclovir (Le et al. 2013; Razonable 2013) Because ganciclovir has antiviral activity against HHV-6, it may prevent disease or reactivation during the first few months posttransplantation, although children who may be seronegative remain at risk for infection after antiviral prophylaxis is complete (Le et al. 2013).

Adenoviruses (AdV)

Adenovirus infections are emergent infections in IT. The reported incidence of AdV infection in IT recipients varied from 4.3% to 57.1%, probably due to lack of systematic screening of all recipients, different diagnostic methods, and use of different study definitions (Florescu et al. 2010; McLaughlin et al. 2003; Parizhskaya et al. 2001; Pinchoff et al. 2003). The majority of AdV infections are reported to be asymptomatic (~78%) (Sandkovsky et al. 2014). Several risk factors for AdV in IT have been documented: younger age, mainly because children are immunologically naïve and are more likely to be exposed to virus (Florescu et al. 2010; Pinchoff et al. 2003; Hoffman 2006); immunosuppressive therapy supported by the highest rate of AdV infections in the first posttransplantation months and by resolution of infection with immunosuppression reduction alone (Florescu et al. 2010; Hoffman 2006).

Most infections occur in the first 6 months posttransplantation (at a median of 1.6 months), but infections have been reported up to 10 years after transplantation (Florescu et al. 2010; McLaughlin et al. 2003; Parizhskaya et al. 2001; Pinchoff et al. 2003; Ziring et al. 2005; Koo et al. 2016). Allograft involvement is relatively frequent, and progression to disseminated disease is not uncommon (Berho et al. 1998; Florescu et al. 2010; Pinchoff et al. 2003). Adenovirus is not an immunomodulatory virus, but through stimulation of the cellular immune response and activation of the cytokine cascade could trigger rejection in IT (Sandkovsky et al. 2014). Common clinical manifestations include enteritis, hepatitis, pneumonia, and disseminated disease (Florescu et al. 2013a; Florescu et al. 2013b). Patients with adenovirus enteritis commonly present with increased stool output and fever (Pinchoff et al. 2003).

AdV culture is not practical from clinical viewpoint (Echavarria 2008). Different immunofluorescence assays are available for rapid diagnosis on respiratory specimens; for rapid diagnosis of AdV in stool samples, immunochromatography, enzyme immunoassays, and latex agglutination tests can be used; however, all these tests are limited by the sensitivity and the number of serotypes that can be detected (Echavarria 2008). For diagnosis and management of AdV infections, mainly AdV viremia qualitative and quantitative PCR can be used. Histopathology remains the gold standard for the diagnosis of tissue-invasive AdV disease. The AdV inclusions can be documented in a high proportion of cases by H&E sections or immunohistochemistry (Koo et al. 2016). In tissue biopsy, adenovirus inclusions ("smudge cells," cells with large basophilic nuclei surrounded by a thin rim of cytoplasm) might be subtle and overlooked (Echavarria 2008; Koo et al. 2016). Presence of lymphoplasmacytic infiltrate in the lamina propria and increased crypt apoptosis, suggestive for adenovirus infection, could be interpreted as acute cellular rejection (Koo et al. 2016; Mehta et al. 2015).

Treatment is mainly based on supportive care and decrease in immunosuppression, when feasible. Although cidofovir is considered the standard treatment for AdV disease, no prospective randomized clinical trials support its use. Two regimens, 5 mg/kg/week or 1 mg/kg/thrice weekly for two consecutive weeks followed by 5 mg/kg every other week, can be used in IT recipients (Florescu et al. 2013a). The main side effects associated with cidofovir administration are bone marrow toxicity and nephrotoxicity (Gilead Sciences 2000). Administration of cidofovir at 1 mg/kg three times per week might be less nephrotoxic, but it might increase the risk of cidofovir resistance and breakthrough herpes virus infections (Hoffman et al. 2001). The dose of cidofovir requires renal adjustment: 0.5 mg/kg three times a week if creatinine clearance is <0.3 mL/min/kg; if the patient is on renal replacement therapy, the procedure needs to be stopped 1 h before and at least 4 h after drug administration (Florescu et al. 2010). To decrease nephrotoxicity, patients should receive pre- and posttreatment fluids (normal saline solution at 5 mL/kg/h) and probenecid (0.5–1.25 g/m^2 3 h before, 2–3 h and 8 h after cidofovir) (Florescu et al. 2010; Hoffman 2006). The length of therapy is not well defined, but it should be continued until symptoms complete

resolution of the symptoms in combination with 3 negative AdV samples collected from the sites that were originally positive (Florescu et al. 2010; Florescu et al. 2013a). Quantitative adenovirus PCR monitoring is useful to assess virologic response and it should be correlated with clinical course (Seidemann et al. 2004). Brincidofovir, a drug still in development, was an effective salvage therapy for AdV disease in highly immunocompromised patients with refractory AdV disease or intolerant to standard therapy in small case series (Florescu et al. 2010). It remain unclear if asymptomatic or transient AdV viremia is associated with increased mortality or graft loss (Florescu et al. 2010; Humar et al. 2005), in contrast with invasive disease (Florescu et al. 2010).

Enteric Viruses

Norovirus

Norovirus are the leading causes of acute nonbacterial gastroenteritis and may present in transplant recipients as severe or protracted diarrheal illness (Florescu et al. 2011; Chong et al. 2016; Silva et al. 2016). Noroviruses, highly stable in the environment and with a low infectious dose (<10 virus particles), can cause infection year round and the outbreaks more frequently during the winter (Lee and Ison 2014). Watery diarrhea is the most common presentation followed by nausea, vomiting, and fever (Florescu et al. 2011; Kaufman et al. 2005; Saif et al. 2011; Chong et al. 2016). Presence of nausea at the time of the diagnosis and CMV infection within the previous 3 months might be independent risk factors for persistent norovirus diarrhea (Chong et al. 2016). Up to 80% of the transplant recipients with norovirus enteritis might require hospitalization, mainly due to severe dehydration (Chong et al. 2016), up to 94% may develop chronic diarrhea, and up to 80% can progress to acute renal failure (Roos-Weil et al. 2011; Saif et al. 2011). Norovirus gastroenteritis seems to be a biphasic illness that has an acute phase with classic diarrhea, nausea, vomiting, and sometimes abdominal pain and fever, followed by the chronic phase characterized by intermittent periods of diarrhea (Lee and Ison 2014). Viral excretion after acquisition of the virus might be prolonged, up to 8 months, posing risks for nosocomial transmission of the virus (Florescu et al. 2011; Kaufman et al. 2005). Noroviruses can be detected in stool, vomitus, or food by quantitative or qualitative reverse transcription PCR (RT-PCR) techniques (Moe et al. 1994; Schwab et al. 1997; Patel et al. 2009). Multiplex PCR has been introduced to detect noroviruses and other gastrointestinal pathogens through a single test (Lee and Ison 2014). Enzyme immunoassay detection methods are available, but they have lower sensitivity and specificity compared with PCR methods (Kele et al. 2011). Differentiating norovirus gastroenteritis from allograft rejection is important for the management; treatment of suspected rejection can worsen and prolong the infection-related symptoms. Histological findings on biopsy consistent with norovirus infection are: blunting of the villi, diffuse infiltrate, mainly with mononuclear infiltrate, and increased crypt apoptosis (Ziring et al. 2005). The majority of patients are managed supportively with hydration, antimotility agents, and dietary manipulations (enteral and/or parenteral support) (Florescu et al. 2008; Chong et al. 2016; Lee et al. 2016). Acute renal failure resolves with intravenous hydration in most of the cases, but decline in renal function has been reported (Lee and Ison 2014). Changes in the dosage of immunosuppressive therapy or to an mTOR inhibitor (sirolimus, everolimus) may speed the resolution of the infection (Kaufman et al. 2005; Chong et al. 2016; Lee and Ison 2014; Saif et al. 2011). Administration of oral immunoglobulins was associated with a favorable trend in resolution of diarrhea and decrease stool output in pediatric and adult IT, but have not shortened hospital stay or decreased cost of hospitalization (Florescu et al. 2011). Nitazoxonide was administered to 50 hospitalized children (25 received placebo and 25 received nitazoxonide) in a small randomized double-blind placebo-controlled trial and it reduced the duration of diarrhea without significant side effects (Rossignol et al. 2006). Currently, there are no vaccines available for norovirus, although several candidate vaccines are in development.

Rotavirus

Rotavirus is one of the most common causes of diarrhea in children, being diagnosed mainly in the winter season in United States. Rotavirus infections in IT have been recently described in case series, with an incidence reported to up to 57% (Adeyi et al. 2010; Eisengart et al. 2009; Ziring et al. 2005). Patients typically present with watery, diarrhea, significant fluid loss, and electrolyte imbalances triggering hospital admission; nausea and vomiting tend to be less pronounced than in patients infected with norovirus (Adeyi et al. 2010; Stelzmueller et al. 2005; Stelzmueller et al. 2007). Most of the time is as a self-limited disease in immunocompetent and immunocompromised patients, but it can be a more prolonged disease in transplant recipients (Adeyi et al. 2010; Fischer et al. 2007). Infection can be diagnosed early after transplantation, within 1 month, or late (reported 2907 days) (Ziring et al. 2005; Adeyi et al. 2010). Prolonged viral excretion (up to 6 weeks) has been documented in transplant recipients (Ziring et al. 2005). In one study, rotavirus enteritis in IT was associated with late cellular rejection, possibly due to stimulation of the cellular immune response and activation of the cytokine cascade by the rotavirus in combination with subtherapeutic tacrolimus levels during the period of diarrhea (Adeyi et al. 2010). Rotavirus infections can be diagnosed with stool rotavirus immune-based assays (latex agglutination, EIA, immunochromatography) in correlation with corresponding clinical symptoms and small bowel biopsy (Bernstein 2009). Multiplex PCR has become more popular diagnostic method since it allows for concomitant screening for a wider range of potential gastrointestinal pathogens. Histology plays an important role in differentiation of rotavirus infection from acute cellular rejection. With rotavirus infections, blunting of the villi, inflammatory infiltrate of the lamina propria, and apoptosis of the epithelium surface are more pronounced in native intestines than in the allograft (Eisengart et al. 2009). Currently there is no anti-rotavirus therapy and treatment is mainly supportive: intravenous fluids, parenteral nutrition, antidiarrheal medications, and adjustment of immunosuppression. Rotavirus vaccines (RotaTeq and Rotarix) are live attenuated virus vaccines and should be administered prior to transplantation. There are limited data regarding the safety or efficacy of rotavirus vaccines in immunocompromised patients (Danzinger-Isakov and Kumar 2009). Rotavirus vaccine can be administered to infants in families with IT recipient; all the members should follow careful hand washing hygiene.

Respiratory Viruses

Almost all respiratory viruses share similar means of transmission (through infectious droplets or contact with fomites), seasonality (peak in the fall and winter months), and clinical manifestations. Transplant recipients are at higher risk for severe infections and complications and may also shed respiratory viruses for longer periods of time, even with the use of antiviral therapy (Englund 2001; Martin et al. 2012; Manuel et al. 2013). Age below 1 year and lower respiratory tract symptoms at presentation seem to be risk factors for poor outcomes (Lo et al. 2013). Influenza and other respiratory viruses have also been linked to allograft rejection (Ison 2007; Stucchi et al. 2010).

Because clinical presentations are not unique to any specific virus (Lo et al. 2013), it is important to obtain samples (nasal washings, nasopharyngeal swabs, bronchial wash specimens) for diagnosis (Manuel et al. 2013). Not all methods for viral identification may be available in some places; culture usually takes longer time and may not identify all viruses. Rapid antigen testing is available for influenza and respiratory syncytial virus (RSV), but the sensitivity of these tests is lower than what is reported by the manufacturer; DFA tests can have similar sensitivities to molecular assays although specific antibodies may not be available for all viruses (Manuel et al. 2013). Molecular assays (multiplex PCR) have great sensitivity and the ability to detect the most important respiratory viruses from a single sample and in a timely fashion (24 h during peak season) (Englund 2001; Ison 2007; Krunic et al. 2007; Kuypers et al. 2006; Tran et al. 2013).

Influenza

Although influenza can be transmitted all year long, its major impact occurs during winter season (Manuel et al. 2013). Risk factors for influenza include: young age, the early post-transplant period, antilymphocyte globulin use, intense immunosuppression, and lymphopenia (Manuel et al. 2013). The 2009 H1N1 pandemic was helpful to better understand risk factors and outcomes in SOT recipients. It has become evident that compared to the general population, SOT recipients have higher risk for severe disease at presentation, complications including pneumonia, bacterial, and fungal infections, allograft dysfunction, and episodes of acute rejection (Ison 2013; Memoli et al. 2014; Minnema et al. 2011). Clinical presentation tends to be nonspecific with fever, headache, and myalgia. In a study of a mixed pediatric and adult population, fever, rhinorrhea, headache, and sore throat were more common in children, while pneumonia was more common in adults; admission rates were similar, but pediatric patients received antiviral therapy sooner and no pediatric mortality was observed (0% vs.7%) (Kumar et al. 2010). Transplant recipients compared with general population are at higher risk of severe complications including viral pneumonia, bacterial infections, myocarditis, or encephalopathy (Lee and Barton 2007) and also tend to have prolonged viral replication and shed virus for loger periods of time (Manuel et al. 2013; Memoli et al. 2014). Delayed antiviral therapy, diabetes mellitus, and use of antithymocyte globulin were all risk factors for severe disease and ICU admission (Kumar et al. 2010).

All patients with known or suspected influenza should be placed on droplet isolation (Manuel et al. 2013). Although efficacy of vaccination may be lower in transplant recipients (Gangappa et al. 2008), it is recommended that all transplant patients receive the annual inactivated influenza vaccine (Danzinger-Isakov and Kumar 2009; Manuel et al. 2013). Use of antiviral therapy is warranted in all IT recipients with suspected influenza, even before microbiological or molecular confirmation, as it has been shown to reduce risk of progression to pneumonia, ICU admission, and death (Ison et al. 2008; Renaud and Campbell 2011; Kumar et al. 2010; Manuel et al. 2013). Only the neuraminidase inhibitors (oseltamivir, zanamivir, and Peramivir) are the preferred agents for both influenza A and B for both treatment and prophylaxis (Manuel et al. 2013). Transplant patients may benefit from antiviral therapy even after 48–96 h and likely require longer duration of therapy, due to prolonged viral replication (Manuel et al. 2013). Resistance to antiviral agents has been described during the 2009 H1N1 outbreak and is a potential concern especially in immunocompromised populations because of prolonged viral shedding (Renaud and Campbell 2011; Ison 2013) and prolonged use of antiviral agents (Memoli et al. 2014).

Parainfluenza (PiV)

PiV shares many clinical manifestations with influenza and other respiratory viruses. It is of particular interest as it can cause severe disease in pediatric SOT recipients (Manuel et al. 2013). Risk factors for infection are similar to those for influenza; however, young age, onset of infection early after transplantation, and profound immunosuppression are risk factors that increase mortality (Apalsch et al. 1995). Because there is no current vaccine or effective antiviral agents to prevent or treat the disease, efforts should be placed on prevention (Manuel et al. 2013). All patients with PiV should be placed on droplet precautions. Antiviral therapy with ribavirin and IVIG are not routinely used, but can be considered in special situations like severe pneumonia (Lee and Barton 2007; Manuel et al. 2013).

Respiratory Syncytial Virus

Respiratory syncytial virus (RSV) is not only the most common respiratory viral infection in children under 1 year of age (Chu et al. 2016), but also the most common in SOT (Lee and Barton 2007), with a rate of 5–50% depending on the type of immunosuppression (Kim et al. 2007). Risk factors for severe disease include prematurity,

infection in children <1 year of age, or underlying lung disease (Manuel et al. 2013). The clinical course can be severe as shown in a few retrospective studies where hospitalization rates ranged between 28% and 75% (Chu et al. 2016; Robinson et al. 2015); one every four required admission to the intensive care unit (Robinson et al. 2015). Transmission is similar to influenza and droplet precautions should be used in all cases. Diagnostic methods available include rapid antigen testing, DFA and PCR detection of respiratory samples (Ison 2007; Razonable 2011; Manuel et al. 2013). Prophylaxis with the monoclonal antibody palivizumab or RSV hyperimmunoglobulin has been shown to be effective in high-risk populations, but data to support its use in IT recipients are lacking (Manuel et al. 2013; Razonable 2011). Many experts recommend its use in patients <1 year or age or on those who are transplanted during RSV season (Manuel et al. 2013). A survey administered among 108 centers in the United States found that of the 67 centers who responded, 33 (49%) reported using palivizumab; most centers used it in patients aged <1 year of age and 80% extended the use for those <2 years of age (Michaels et al. 2009). In severe infections, it is vital to attempt a reduction in immunosuppression. Ribavirin is approved for use in high-risk children with RSV, and it may be used either orally or by inhalation or combined with IVIG depending on the center (Beaird et al. 2016), but data on its use in IT recipients are limited (Lee and Barton 2007). Antiviral therapy with ribavirin may reduce mortality with greater reductions when combined with palivizumab of RSV-IVIG (Vilchez et al. 2003; Manuel et al. 2013). Aerosolized ribavirin can be used, although its use is limited by potential side effects to the person administering the medicine (headache, conjunctivitis, rhinitis, rash, dizziness, lacrimation; teratogenicity, and embriocidal potential) and also to patients who may experience bronchospasm, worsening respiratory status, apnea, and atelectasis. In mechanically ventilated children receiving ribavirin, the endotracheal tubes should be suctioned every 1–2 h to minimize the risk of drug precipitation in the system and ventilator dysfunction. Oral administration may be an alternative in high risk patients (Keck et al. 2012; Pelaez et al. 2009).

Human Metapneumovirus

Human metapneumovirus (hMPV) is closely related to RSV and can cause upper and lower respiratory tract infections (Manuel et al. 2013). Infection rates may be similar to the ones for influenza, RSV and PiV (Lee and Barton 2007). Infection usually presents as a nonspecific upper respiratory illness but may manifest initially as tracheobronchitis or pneumonia in about 10% patients. Rates of pneumonia may sometimes be higher and could require high oxygen supplementation or admission to the intensive care unit in more severe cases (Chu et al. 2014). Diagnosis is based on the detection of the virus with multiplex PCR. Supportive therapy and reduction of immunosuppression are the mainstay of therapy, although in certain severe cases ribavirin with or without IVIG have been used (Chu et al. 2014; Manuel et al. 2013).

Rhinovirus

Although it is usually a self-limited disease in immunocompetent individuals, human rhinovirus can be a significant cause of morbidity in SOT patients (Tran et al. 2013). Prolonged viral shedding is usually seen in SOT recipients and may pose a risk for nosocomial transmission and outbreaks, although the clinical implications are not yet fully understood (Manuel et al. 2013).

Conclusions

Opportunistic viral infections cause significant morbidity and mortality among IT recipients. Management of these infections is sometimes more difficult due to lower age of the patients and use of more intense immunosuppression, compared to other solid organ transplants.

Management is often extrapolated from other SOT recipients as data for management of many of these infections are limited in IT. Because the graft may be involved more frequently, a high level of attention and care is needed in order to diagnose and treat early in order to preserve graft function. The mainstay of management should always include a reduction in immunosuppression when feasible. Although there are several new drugs in development to help treat these infections, the current armamentarium is limited to only a handful of drugs. Preventive vaccines are urgently needed as only influenza vaccination is currently recommended after transplantation.

Cross-References

- ▶ Pathology of Intestinal Transplantation
- ▶ Pharmacologic Considerations in Multivisceral Transplantation
- ▶ The Role of the Transplant Administrator

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Autotransplantation

Peter Liou, Adam Griesemer, and Tomoaki Kato

Contents

Abstract

Certain abdominal tumors involving the mesenteric root and major vasculature are generally considered unresectable with conventional surgical approaches. Using techniques developed for abdominal organ transplantation, surgeons have successfully resected such tumors in cold preservation solution after removing the tumor-visceral bloc, followed by reimplantation of the involved organs. This method, known as ex vivo resection and autotransplantation, can allow for margin-free resection and complex vascular reconstruction in carefully selected patients. The perioperative management and surgical technique of intestinal and multivisceral autotransplantation is described in this chapter.

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Autotransplantation · Ex vivo tumor resection · Intestinal transplantation · Multivisceral transplantation · Mesenteric tumor · Autograft

Introduction

Tumors involving or encasing major abdominal vasculature have long since plagued surgeons, and many are deemed unresectable by standard conventions. Recent advances and experience in intestinal and multivisceral transplantation have contributed new approaches to these types of tumors – that of ex vivo surgery and autotransplantation.

The concept of ex vivo resection and autotransplantation of abdominal organs is not new. Resection and reimplantation of a kidney was first described by James Hardy in 1963 as a salvage technique following a high ureteral injury (Hardy 1963). The success of this surgery sparked a particular interest in renal autotransplantation for various other indications, including renovascular and ureteral disease requiring complex reconstruction, or even centrally located tumors in patients with solitary kidneys. Several decades later, Rudolf Pichlmayr subsequently extended the same principle to the liver in attempt to resect tumors located in critical areas such as the hepatic venous confluens or the porta hepatis (Pichlmayr et al. 1995).

Years later, drawing from techniques gained from intestinal transplantation in conjunction with ex vivo concepts, Andreas Tzakis and his group in Miami reported the first successful intestinal autotransplantation following the resection of a large fibroma involving the mesenteric root (Tzakis et al. 2000). Since then, an additional 30 cases have been reported worldwide for tumors involving the superior mesenteric vessels (Wu et al. 2016b) along with five multivisceral ex vivo resections involving both the superior mesenteric artery and the celiac axis (Kato et al. 2012).

The limited overall experience testifies to the relatively restricted indications of the technique, as well as a considerable amount of specialized multidisciplinary care required. For the carefully selected patient however, the potential benefits of intestinal autotransplantation in the resection of tumors involving mesenteric vessels are significant. Traditional surgical approaches to mesenteric tumors are associated with risks of massive enterectomies leading to short bowel syndrome, intestinal ischemia, as well as incomplete tumor removal. Ex vivo techniques enable access to the entire mesenteric root while assuring visceral preservation, thereby allowing the possibility of a complete tumor resection and major vascular reconstruction, minimizing the concern for end organ ischemic injury (Tzakis et al. 2002, Selvaggi et al. 2004). Successful autotransplantation could furthermore prevent the necessity of allotransplantation and its associated morbidities (Moon et al. 2005). In this chapter, the perioperative and technical considerations of intestinal and multivisceral autotransplantation will be described.

Indications for Autotransplantation

As the experience for autotransplantation is still limited, clear indications have yet to be defined. Today, intestinal or multivisceral autotransplantation is almost exclusively utilized in the assistance of tumor resections involving the mesenteric root. The ideal candidate for intestinal autotransplantation is a patient with a benign or slow growing but symptomatic mass involving the mesenteric root that otherwise would be difficult or impossible to remove by conventional surgical methods. Patients often present with abdominal pain, early satiety, symptoms of obstruction, gastrointestinal bleeding, or sequelae of portal hypertension. Candidate tumor types include desmoid tumors (Tzvetanov et al. 2012), fibromas, ganglioneuromas, vascular dysplasias, and pancreatic solid pseudopapillary neoplasms (Tzakis et al. 2012). Ex vivo intestinal resections have been performed on all of these pathologies with excellent reported long-term outcomes.

A second group of patients have malignant disease. Several tumors types, including the retroperitoneal soft tissue sarcomas (liposarcoma and leiomyosarcoma) or carcinoid tumor may be amenable for ex vivo resection with acceptable long-term survival (Kitchens et al. 2011, Tzakis et al. 2003). For patients with locally advanced sarcomas, the primary oncologic goal and potential cure

is by achieving a complete tumor resection. But for tumors involving the mesenteric root or major vascular structures, the probability of achieving an R0 resection is low. Therefore, for carefully selected patients, ex vivo techniques can maximize the opportunity for a complete resection by providing wide access to the mesenteric root while minimizing the need for collateral visceral resections.

On the other hand, the role of ex vivo resection in patients with pancreatic adenocarcinomas or other intestinal adenocarcinomas involving the superior mesenteric artery (SMA) is largely unclear (Quintini et al. 2007; Wu 2016b). Since complete surgical resection remains the only hope for reasonable long-term survival, there have been attempts to expand the realm of resectable disease, including tumors that involve the SMA. However, pancreatectomy with arterial resection has been associated with major perioperative morbidity and mortality, owing to complications including vascular thrombosis as well as liver and intestinal ischemia (Mollberg et al. 2011). In these cases, ex vivo resection offers a theoretical technical advantage of allowing the resection of involved vessels as well as its reconstruction in a more controlled setting with prolonged visceral preservation. But perhaps owing to already micro disseminated disease, the few reported ex vivo pancreatic resections for ductal adenocarcinoma have been associated with limited long-term survival. Currently, patients with pancreatic adenocarcinoma and mesenteric arterial involvement should probably not be considered a routine indication for ex vivo resection and autotransplantation. For the select few who present at a young age with little to no comorbidities and local disease, advanced discussions must be held weighing the benefits and risks of major surgery with potentially delayed adjuvant chemotherapy versus chemotherapy alone, in specific regard to survival and quality of life.

Preoperative Evaluation and Screening

Candidates for intestinal autotransplantation often have been evaluated at multiple medical institutions prior to surgical referral. As a result, they will have already undergone numerous medical studies and imaging, which will need to be obtained and thoroughly examined prior to consideration for surgery. It is recommended that intestinal autotransplantation only be performed at institutions experienced in intestinal transplantation techniques and are able to rapidly evaluate for allotransplantation as backup in the setting of complications resulting in graft loss (Nikeghbalian et al. 2014).

Patients are required to undergo a complete medical and surgical evaluation under the auspices of a multidisciplinary care team which includes the surgeon, a gastroenterologist specializing in bowel rehabilitation and transplant, a medical oncologist, nutritionist, social worker, and other medical specialists such as infectious disease and cardiology as necessary. Patient factors, such as age, functional status, cardiopulmonary status, comorbidities, and adequate psychosocial support, will need to be considered prior to proceeding with surgery.

Patients sometimes present with a complex surgical history. Many have undergone prior laparotomies with attempted tumor or bowel resections and intestinal bypass procedures. Due to chronic obstruction, patients are sometimes malnutritioned and dependent on direct enteral feeding or parenteral nutrition. Those that have developed portovenous thrombotic complications often undergo surgical shunt or TIPS procedures prior to referral.

Imaging is the most critical part of the surgical planning process and usually consists of an abdominopelvic CT scan with intravenous contrast to evaluate the relevant anatomy and vessel involvement (Fig. 1). In select cases where mesenteric vascular anatomy is unclear, angiography can be performed to guide eventual reconstruction. It is also important to estimate the remaining small bowel length, and how much bowel can be salvaged. Abdominal MRI is an appropriate alternative but often does not contribute additional information. Appropriate imaging studies to exclude metastatic disease are also necessary.

Tissue diagnosis is usually available from biopsies obtained during prior surgical exploration or diagnostic endoscopy and help guide neoadjuvant chemoradiation as determined by the

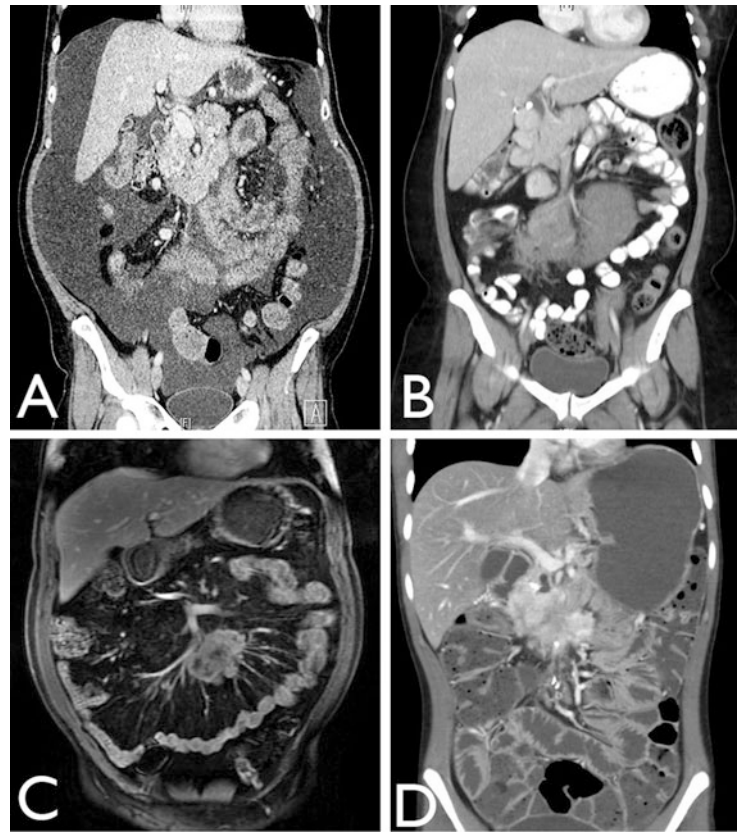

Fig. 1 (**A**–**D**) Four examples of mesenteric tumors that were removed by ex vivo resection and intestinal autotransplantation

tumor type. For patients that have no tissue available, image-guided peripheral or endoscopic biopsies are safe and valuable in determining management options.

Surgical Techniques

Intestinal Autotransplant

For tumors involving only the mesenteric vasculature without extension into adjacent organs, it is possible to perform an isolated intestinal autotransplant without pancreaticoduodenectomy. The abdomen is exposed with a generous midline incision and subcostal extension if necessary. Adhesions may often be present from prior exploration and preoperative radiation but must be carefully lysed. A general survey of the abdomen is carried out to assess for evidence of metastatic disease. Once the decision is made to proceed with autotransplantation, the tumor is carefully dissected off of its retroperitoneal attachments. The small intestine and colon are first mobilized. The tumor sometimes extends into the pelvis and should be removed from the pelvic wall while carefully preserving the ureters. In order to avoid tumor spillage, it may sometimes be prudent to *first* isolate a segment (or segments) of bowel along with their associated arterial branches and flush with cold preservation solution prior to completing the tumor resection, similar to the technique of living donor intestinal transplantation (Fig. 2). Once the tumor-intestinal complex is mobilized, the proximal jejunum and transverse colon are divided leaving the entire bloc attached only by the superior mesenteric artery and vein (SMA and SMV). After a heparin bolus is given, the SMA is transected at its take off from aorta, leaving 1–2 mm of cuff if possible. The level of portomesenteric transection is dependent on the location of the tumor. Once the specimen is

removed, it is immediately flushed with preservation solution and placed in an ice bath utilizing standard preservation technique. Ex vivo resection is then carried out in a bloodless field (Fig. 3) and vascular reconstruction performed as necessary. The entire mesenteric vasculature is carefully assessed for tumor involvement, including the jejunal and ileal branches as well as the ileocolic vessels. If distal tertiary branches are involved, the associated bowel may have to be sacrificed at this time. If the proximal main trunks of the SMA or SMV are resected, extension grafts can be created with harvested recipient internal iliac artery and internal jugular vein. At the time of back table resection, another "recipient" team is working to achieve hemostasis or perform other necessary procedures, such as lymphadenectomy or vascular shunting (Fig. 4).

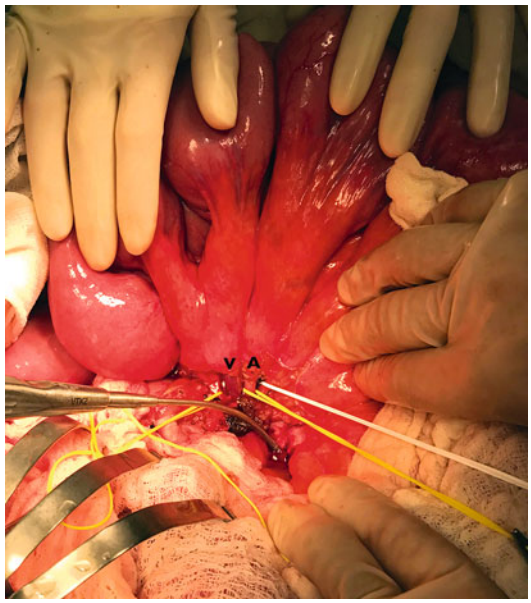

Fig. 2 Isolation of the arterial (*A*) and venous (*V*) pedicle for a segment of jejunum that will later be used for reimplantation after tumor removal

Once the autograft is prepared, it is brought to the field for implantation (Fig. 5). The SMA or reconstructed arterial branches are anastomosed to the retained SMA stump or infrarenal aorta. Subsequently, the SMV or reconstructed venous branches are reconnected to the portal vein (Fig. 6). If this is not possible due to portal venous thrombosis, the SMV can be anastomosed directly onto the inferior vena cava. For tumors with involvement of the secondary or tertiary venous

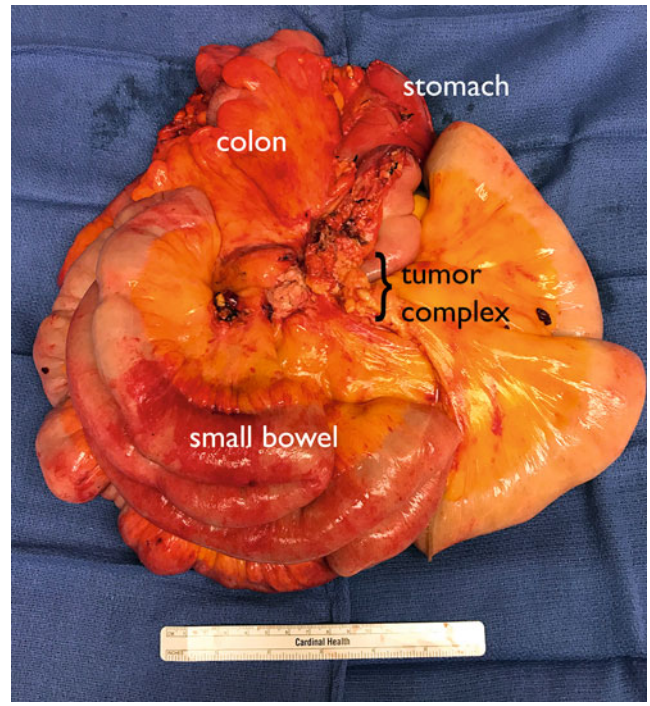

Fig. 3 Example of a removed mesenteric tumor specimen during ex vivo resection that includes part of stomach, duodenum, head of pancreas, small bowel, and ascending colon. The segment of small bowel used for reimplantation has already been removed in this photograph

branches, it is possible to reconstruct the outflow conduit with prosthetic graft. The graft is then reperfused (Fig. 7) and intestinal viability evaluated. Occasionally, further bowel resection is required due to lack of adequate perfusion from reconstructed arterial branches. If perfusion of the bowel is questionable, use of intraoperative indocyanine green fluorescence angiography can be performed. The base of the mesentery is then fixed and hemostasis achieved. Gastrointestinal continuity is then restored with jejunojejunal and ileocolonic anastomoses, and a temporary Santulli type "chimney" ileostomy is performed. Gastrostomy tube placement, appendectomy, and cholecystectomy are routinely performed in all autotransplantation cases.

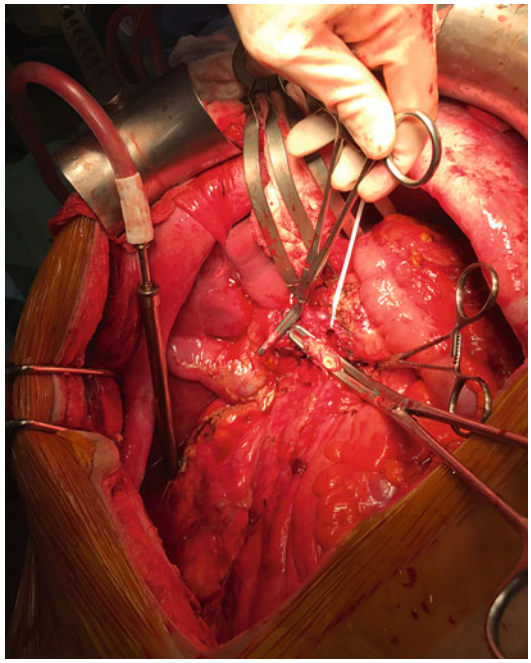

Fig. 4 The abdomen after removal of the intestine/tumor complex and wide exposure of the retroperitoneum and mesenteric vasculature

Intestinal Autotransplant with Pancreaticoduodenectomy

For patients with mesenteric tumors originating from or involving the pancreas, a pancreaticoduodenectomy or total pancreatectomy would also be performed. The abdomen is explored in the routine fashion and examined for metastatic disease. The colon and duodenum are extensively mobilized and the pancreas rotated to facilitate exposure of mesenteric root. If ex vivo resection is decided to be feasible, the gastrointestinal tract is divided at the distal stomach and transverse colon, and the gastroduodenal artery and common bile duct are ligated. The pancreas is transected, further exposing the SMV and SMA. If the entire pancreas is to be removed, the splenic artery and short gastric vessels are ligated as well. The organ block consisting of the

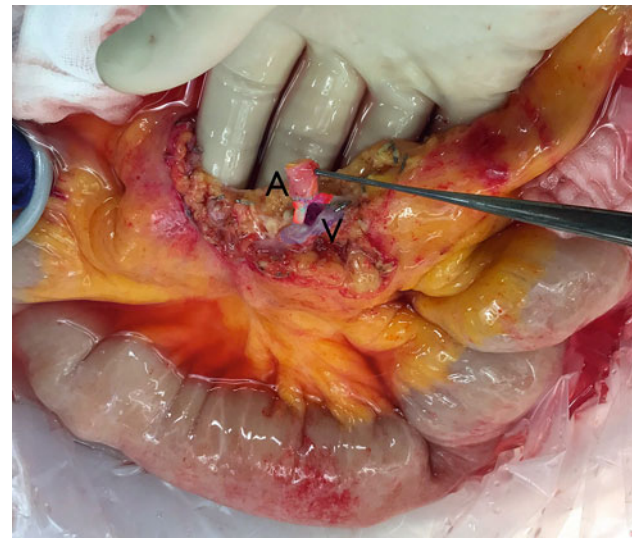

Fig. 5 Prepared autograft in cold preservation. Two arterial branches (*A*) have been reconnected with a segment of the patient's own internal iliac artery for implantation to the SMA. Also depicted (*V*) are the segmental venous branches that will be anastomosed with the portal vein

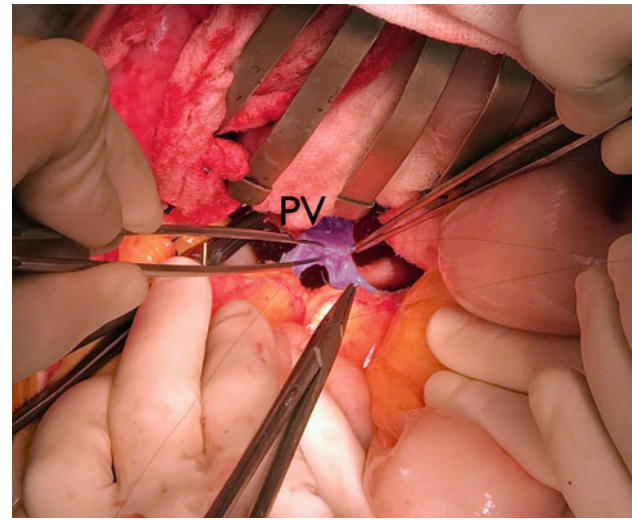

Fig. 6 Anastomosis of the venous segmental branches to the portal vein (*PV*)

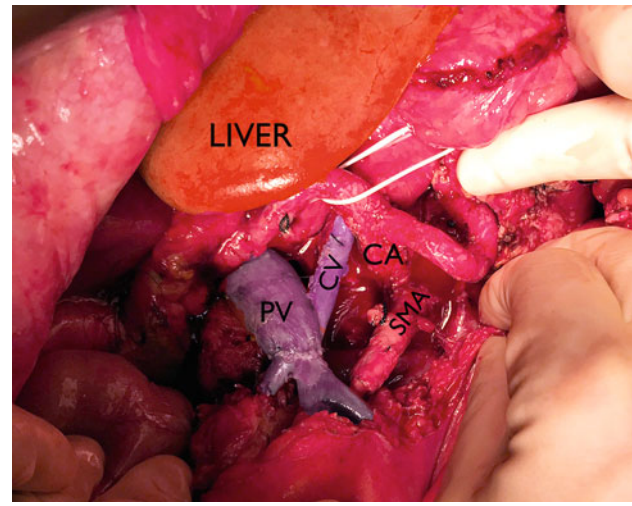

Fig. 7 Reconstructed mesenteric vasculature following bowel reperfusion. The portal vein (*PV*) and superior mesenteric artery (*SMA*) are connected to segmental mesenteric vessels. The celiac trunk (*CA*) and its affiliated branches are shown above. The coronary vein (*CV*) is seen coming off the PV

distal stomach, small bowel, pancreas, and part of the colon are suspended from the SMA and SMV which are subsequently divided. If the SMV is solely involved, it can be transected at its origin. Sometimes the portomesenteric junction is involved and must be resected with the tumor. If there is insufficient length to reconnect the splenic vein to the portal vein, a distal splenorenal shunt can be performed (Fig. 8).

Once the tumor is removed in the cold, arterial and venous reconstructions can be performed and autotransplanted as described above. Gastrointestinal reconstruction follows standard techniques described in the Whipple procedure. A pancreaticojejunostomy or pancreaticogastrostomy is created unless a total pancreatectomy was performed. Due to recent studies suggesting lower postoperative pancreatic and biliary leak rates, a pancreaticogastrostomy may be preferred (Menahem et al. 2015). If there is concern for adequate graft perfusion, the operation can be suspended temporarily and a second-look laparotomy performed 12–24 h later with completion of the gastrointestinal reconstruction. A choledochojejunostomy and gastrojejunostomy is constructed in standard fashion, with placement of a gastrostomy tube. The distal small bowel or colon from the graft is then anastomosed to the remaining colon and a

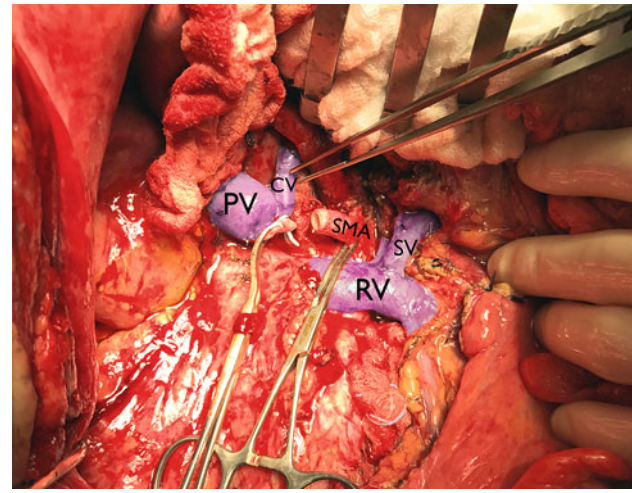

Fig. 8 Prepared stump of the superior mesenteric artery (*SMA*) and portal vein (*PV*) used for intestinal autotransplantation. In this example, a distal splenorenal shunt (*SV* and *RV*) was performed to drain the distal splenic vein (Coronary vein, *CV*)

Santulli type enterostomy is fashioned. If adequate distal bowel perfusion is a concern where only a segment of small bowel was salvaged, creation of an end ileostomy leaving a distal colonic Hartmann-type stump without anastomosis is reasonable.

Multivisceral Autotransplant

Select tumors that involve both the roots of the celiac and SMA are amenable to a multivisceral ex vivo resection with autotransplantation (Kato et al. 2012). The techniques of this complex and variable procedure are derived from experience in multivisceral allotransplantation. As with any ex vivo procedure, vascular reconstruction and salvageability of individual organs are decided by tumor location and involvement. As vascular reconstructions tend to be more extensive in multivisceral resections, synthetic vascular grafts are often used in lieu of autologous tissue.

If multivisceral resection is deemed feasible at the time of exploration, the abdominal viscera are mobilized and divided at the gastroesophageal junction and distal to the splenic flexure. The kidneys and distal colon are left in situ unless there is evidence of tumor involvement. Once the abdominal contents are mobilized off the retroperitoneum, the vascular pedicle is developed at the roots of the celiac artery and SMA, transecting both just 1–2 mm distal to their origins. The liver, which has been mobilized off the IVC, is removed from the body with the ligation of the major hepatic veins in a single cuff. If it is not possible to isolate these vascular pedicles due to tumor involvement, segments of the aorta and IVC can be removed en bloc with the specimen and reconstructed with synthetic graft as the tumor is resected in the back table. Veno-veno or veno-arterial bypass would need to be considered but is usually not necessary. If the aorta or vena cava is removed at the level of the renal vessels, reimplantation would be performed during reconstruction with synthetic graft. If the native IVC is left in situ, a synthetic patch can be temporarily sewn onto the vena cava at the hepatic venous orifice to allow full unclamping of the vessel during back table resection.

The strategy of back table resection and reconstruction is variable and must be individualized to tumor location and involvement. After thorough evaluation of the vasculature for tumor infiltration, organs deemed unsalvageable are removed, which can include the stomach, spleen, pancreas, as well as segments of the small or large intestine. Once the tumor is completely resected, the remaining organs are then reimplanted. The common hepatic artery and SMA are reconnected via synthetic grafts either to existing vascular stumps or the reconstructed aorta (Fig. 9). The splenic and left gastric arteries can be sacrificed without compromise to perfusion in the stomach, spleen, or pancreas. Venous reconstruction is performed reconnecting the hepatic veins to the IVC. Tumor infiltrating the hilum poses a more significant

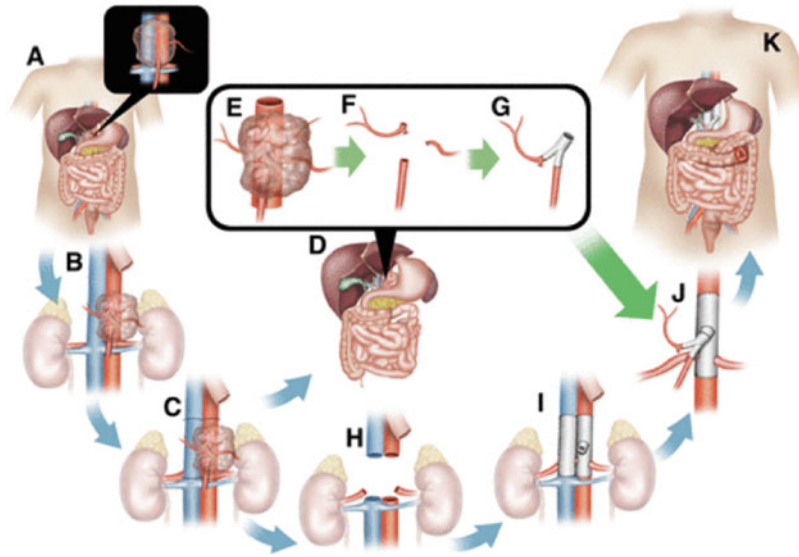

Fig. 9 An illustrated example of a multivisceral ex-vivo resection for a tumor involving the abdominal aorta and the roots of the celiac artery and the SMA. In this case, the hepatic artery and SMA were reconstructed using a Y-shaped synthetic vascular graft (Permission from Wiley)

challenge and may require additional vascular and biliary reconstruction. In these cases, the liver is implanted separately from the gastrointestinal complex, and a renoportal anastomosis created to restore portal flow **(**Fig. 10**)**. Once the organs are reperfused, intestinal reconstruction is carried out in standard fashion as described above.

Postoperative Care

Patients are routinely transferred to the intensive care unit for postoperative monitoring. Hemodynamics and standard laboratory values including lactate are trended carefully, with a low threshold for exploration in the setting of concern for bleeding or inadequate graft perfusion. Doppler ultrasound is performed immediately postoperatively to evaluate the mesenteric and hepatic vasculature. A heparin drip is initiated once there is no concern for bleeding, usually within 24 h after surgery and transitioned eventually to aspirin when tolerating enteral feeding. Insulin is administered as needed, especially if a total pancreatectomy was performed. Outputs are monitored carefully and replaced as necessary. Total parenteral nutrition is initiated postoperatively and tapered with initiation of enteral feeding, usually 1 week after surgery. Titration of enteral nutrition is highly dependent upon the patient's postoperative course and remaining anatomy and should be managed by those experienced in nutrition for intestinal transplant patients. Initial intestinal output is typically high (in the range 2–3 l per day) but should decrease over the course of several weeks. Antimotility agents can be added gradually as needed. The stoma is usually closed 2–3 months after surgery.

Complications

As with any intestinal or multivisceral allotransplant, the morbidity of intestinal ex vivo resection and autotransplantation is significant. Many associated risks are similar to other major abdominal surgeries, including significant bleeding, abdominal sepsis, or intestinal/pancreatic anastomotic leakage or fistulae. Perhaps the most devastating transplant-specific complication is loss of the autograft as a result of inadequate perfusion, most commonly from vascular thrombosis or arterial dissection (Kato et al. 2012). Data are still inconclusive pertaining to the best methods of preventing vascular thrombosis, but until more studies are completed, it is reasonable to initiate anticoagulation therapy routinely for all patients who have undergone autotransplantation, especially those that required synthetic graft placement (Wu et al. 2016). Patients with thrombosis or dissection resulting in graft loss will

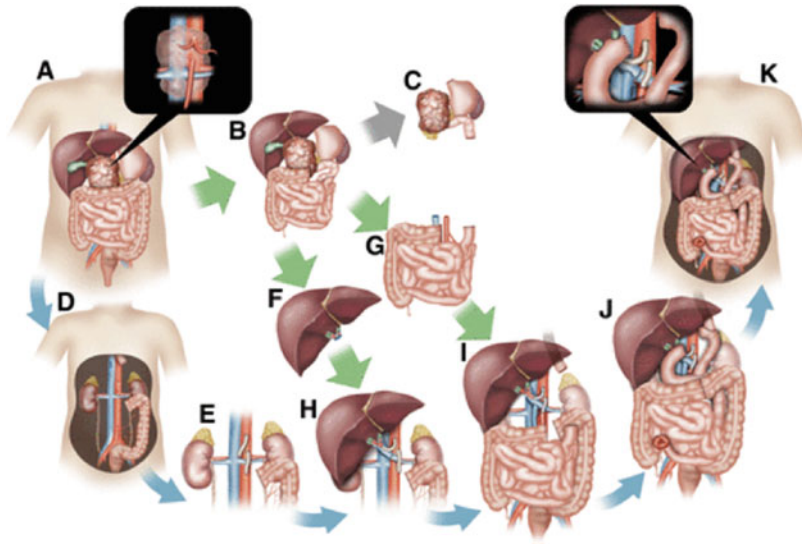

Fig. 10 A second illustrated example of a multivisceral ex-vivo resection for a tumor occupying the entire pancreas, with involvement of the celiac artery and SMA. The liver was reimplanted separately using inflow from the left renal vein with an interpositional jugular vein graft. The intestine was then implanted connecting autograft SMV to the side of jugular vein graft (Permission from Wiley)

require urgent allotransplantation. Long-term complications of vascular perfusion including anastomotic stenosis may be amenable to endovascular or surgical intervention.

Another major consideration is reimplanting an adequate length of bowel to maintain sufficient nutritional and fluid absorption. With proximal positioning of tumors on the mesenteric root, the entire small bowel is usually able to be reimplanted without concern of bowel length inadequacy. As previously mentioned, tumor infiltration more distally into the bowel mesentery will require preservation of isolated bowel segments in order to achieve complete tumor resection. In this case, reconstruction of the mesenteric vasculature becomes more challenging, particularly in constructing the venous outflow tract. If the bowel length is not sufficient to maintain adequate nutrient absorption (typically less than 100 cm) without parenteral nutrition, the patient should be referred for intestinal allotransplantation in the appropriate context.

Conclusions

Ex vivo intestinal resection and autotransplantation lends techniques developed for allotransplantation to permit the removal of mesenteric tumors otherwise deemed unresectable by standard convention. By allowing reconstruction of critical vasculature in the safety of cold organ preservation, the complete resection of almost any locally invasive mesenteric tumor is made technically feasible. Of course, the employment of this technique should be reserved to a few tumor types after a thorough discussion of the risks and benefits of attempting such a procedure with the patient and multidisciplinary provider team. And despite the oncologic promises of ex vivo resection, the procedure still carries significant morbidity even when performed at the most experienced centers. But for the carefully selected patient, the advantages of ex vivo resection and autotransplantation, including a complete tumor removal without the need for lifelong immunosuppression, are remarkable.

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The Role of the Transplant Administrator

Alexander Aussi

Contents

Abstract

The transplant process is a labor-intensive experience for any patient. Aside from careful patient selection and an unwavering patient commitment to a long-term and complex medical regimen, all end-stage organ failure patients considering transplantation as an option of care will interact with a multidisciplinary professional team of clinical specialists who bring about their unique experiences from different specialties. A successful transplant program is one that is able to translate this multidisciplinary approach to a coordinated, cohesive, and contemporary transplant care with excellent outcomes. We examine the role of the transplant administrator who is tasked with developing administrative policies to organize overall care being provided, where all specialists function based on a preapproved and adhered to set of protocols in an interactive and highly regulated healthcare environment.

Keywords

Competency(ies) – an ability or skill · CoPs – Medicare's conditions of participation · CTC – Medicare and UNOS certified transplant center · DRG – Diagnosis Related Group · ESRD – End-stage renal disease · NOTA – The National Organ Transplant Act · OAC – Organ acquisition costs · OPTN – Organ procurement and transplantation network · Transplant process – The four phases of transplantation · UNOS – The United Network for Organ Sharing

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Introduction

The transplant administrator is a senior-level administrative professional with broad responsibilities for the administration and operation of the transplant center. This role entails the coordination of inpatient and outpatient care, serving as liaison with the Medical Center and Medical Group physician services. The administrator is responsible for planning, organizing, directing, and controlling of the 24/7 operations of the transplant center in order to meet the needs of all patients, their families, and physicians including the oversight of clinical operations, in addition to the business, personnel, financial, and budgetary aspects of care in a complex and highly regulated framework.

While the role of the transplant administrator may change from a healthcare institution to another, some constants remain, such as professional attitude and maturity, advanced clinical and administrative credentials, and the ability to relate to multiple people from diverse backgrounds.

The Role of the Transplant Administrator

A Review of the Transplant Regulatory Environment – UNOS and CMS

In 1984, the United Network for Organ Sharing ("UNOS") was formed as an independent, nonprofit organization servicing the cause of organ donation and transplantation.

Also in 1984, the National Organ Transplant Act ("NOTA") (National Organ Transplant Act (NOTA) 1984) called for an Organ Procurement and Transplantation Network ("OPTN") (The Organ Procurement and Transplant Network (OPTN) 1985) to be created and run by a private, nonprofit organization under federal contract and provided a framework for the structure and expectations of the OPTN.

UNOS was first awarded the national OPTN contract in 1986 by the U.S. Department of Health and Human Services and remains as the organization to ever operate the OPTN.

Medicare approved payment for renal dialysis and kidney transplantation on June 3, 1976 as the sole payer for dialysis and transplant services then. Kidney transplant centers participated in the Medicare program by meeting requirements set forth at 42 CFR Part 405, subpart U, "Conditions for Coverage of Suppliers of End Stage Renal Disease ("ESRD") Services (Conditions for Coverage of Suppliers of End Stage Renal Disease (ESRD) Services 2012). Those requirements formed the initial set of rules that a transplant center should meet to qualify for payment on transplant services rendered.

Beginning in 1987, extra renal programs notably heart, lung, liver pancreas, and intestines were approved based on National Coverage Determinations ("NCDs") which are based on the "reasonable and necessary" provision of the Medicare statute (section 1862(a)(1)(A) of the Social Security Act). Transplantation of extra-renal organs will only be approved for payment in centers which met the complex requirements set forth in each NCD. Medicare remains the largest payer for organ transplant services at any center in the United States.

On March 30, 2007, the Center for Medicare and Medicaid services, commissioned by Congress, released its new rule on conditions of participation (CoPs) for heart, heart–lung, intestine, kidney, liver, lung, and pancreas transplant centers. (Hospital Conditions of Participation: Requirements for Approval and Re-Approval of Transplant Centers to Perform Organ Transplants; Final Rule 2007.) This rule was created to set clear expectations for safe, high-quality transplant service delivery in Medicare-approved facilities and to establish a uniform approach to transplant program survey and certification.

The new CoPs were made effective June 28, 2007. All transplant programs were required to file for initial recertification, and outcomes are now monitored regularly with strict enforcement proceedings in case of failure to comply with outcome requirements set forth in the CoPs.

Phases of the Universal Transplant Process

Most providers in the Transplant field agree that the Transplant process is comprised of four distinct phases:

Phase 1 – referral and evaluation – includes all program health services and professional fees required to assess and evaluate a patient for acceptance into the hospital's transplant program. Phase 1 ends when the patient's name is added to the transplant waiting list with the United Network for Organ Sharing (UNOS). For live donors, Phase 1 ends upon the patient's acceptance into the program. For patients who do not progress to have their name added to the wait list, Phase 1 ends when the program's selection committee determines they are not a candidate for transplantation.

Phase 2 – listing, wait, and health maintenance – includes all program health services and professional fees provided to a patient following acceptance into the transplant program, or addition to the waiting list and before the actual transplant.

Phase 3 – actual transplant admission – includes all transplant health services and professional fees provided to a patient and/or living donor during the transplant until the earlier of the patient's and live donor's first discharge from the hospital or transfer to another facility (e.g., rehabilitation unit, skilled nursing, etc.).

Phase 4 – posttransplant care – includes all transplant health services and professional fees provided to a patient during the first year immediately following Phase 3.

The transplant process is a labor-intensive experience for the patient and program. Aside from careful patient selection and an unwavering patient commitment to a long-term and complex medical regimen, the four phases require staff dedication and incremental resources, the level of which commensurate with the volume of patients being evaluated and the annual number of patients being successfully transplanted. As volumes increase, there is always a need to assess the program's labor and other support services to ensure complex and immune-suppressed patients are properly and promptly cared for.

The Transplant Administrator

Like in an orchestra, all clinical specialists (players) bring about their unique experiences from different specialties (tunes from sets and instruments). When played individually, those tunes may not translate to coordinated, cohesive, and contemporary transplant care (a masterpiece of music). The transplant administrator as the Orchestra's conductor is a mature individual with excellent communication skills who is capable of working in an interactive administrative environment. The transplant administrator, in close coordination with the program clinical directors, creates the environment and policies to organize care being provided, where all specialists function based on a preapproved and adhered to set of protocols. Great music will then follow.

For a transplant administrator to succeed in their role, they need to develop competencies in four areas as follows.

The Cure Versus Care Concepts – A Constant Struggle

Hospitals are traditionally focused on a cure for sick patients. Most hospitals' primary operating model is to get sick patients in, cure them, then get them out. Medicare and most insurance companies in the United States pay for inpatient services under the Diagnosis Related Groups ("DRG") system, which is a flat sum of money per diagnosis code. Aided by case managers, social workers, and financial counselors, hospitals strive to create a more efficient admission and discharge processes, for the overall betterment of the length of stay per admission DRG, which in turn translates into a better margin per case. Sophisticated cost accounting software now help hospitals quantify the number of staff hours and supply cost needed for each of the hospital DRGs on a regular basis.

Transplant programs look at the concept of "curing" patients as one of the four phases, Phase 3 to be exact. This is when a patient on the waiting list is called in to receive the organ transplant. There is always a constant struggle between the concept of "curing" a patient and "caring" for the patient through all four phases of the transplant process. It takes a special type of

a transplant administrator to justify the need for resources required from a multidisciplinary cadre of professionals in support of patients through all phases of transplant. The transplant administrator will constantly bump against limited metrics available in hospital cost accounting departments to justify growth and changing needs. The transplant administrator must be able to identify missing resources and understand it. The administrator must also be able to connect with the clinical team from multiple specialties and clinical backgrounds and must be comfortable in approaching hospital administration with a business plan for the most safe and economic way to meet the need.

The transplant administrator ensures the attainment of objectives through the selection, development, organization, motivation, management, evaluation, promotion, and deployment of human resources; and the establishment, maintenance and utilization of facilities, equipment, supplies, outside vendors, and other required resources. The transplant administrator works closely with hospital and medical group's leaders to approve and obtain optimal administration, financial performance, staffing, and integration of transplant care across the inpatient and outpatient venues.

Fiscal Management: The Role of the Medicare Transplant Cost Report

Medicare reimburses certified transplant centers ("CTC") for the reasonable and necessary costs associated with acquiring an organ for a patient. These costs are called organ acquisition costs ("OAC") (Medicare Provider Reimbursement Manual Part 1 – Chapter 31, Organ Acquisition Payment Policy 2012). Organ acquisition service costs are acquired during Phases 1 – evaluation and 2 – wait period of the universal transplant process for potential recipients and in phases 1, 2, and 3 for living donors (effective Mar 2012).

OACs include a broad range of costs, the largest of which are the tissue typing and crossmatch services including services furnished by independent laboratories, living donor and recipient completed clinical evaluations, and direct costs of transplant personnel, primary salary, and benefits of clinical and administrative staff assigned for pretransplant and outreach or education activities.

OACs incurred by the CTC are paid to the CTC's hospital using an end-of-year reconciliation through the hospital's cost report. The pretransplant evaluation process and waitlist period are "cost reimbursed" for Medicare's portion of the cost of operating the pretransplant departments (Medicare Provider Reimbursement Manual Part 1 – Chapter 31, Organ Acquisition Payment Policy 2012). For non-Medicare primary payer patients, the transplant center must charge the non-Medicare primary payer enough or contract with the payer in such a way as to ensure that the transplant center will be paid enough to cover each patient's proportionate share of the cost of operating the pretransplant departments. If the hospital's Medicare cost report is completed properly and the contracting and billing process are completed properly, the transplant center should recover the full cost of the pretransplant evaluation process with a positive margin. However, there are a few exceptions to this rule because of Medicaid and other "governmental" payer programs.

The pretransplant evaluation process not only includes the workups for patients who were actually transplanted but also the workups for potential recipients and potential living donors who were evaluated and not accepted in the program, plus the number of patients on the waiting list. Any medical interventions or treatments that are necessary to keep the patient healthy while in the waiting period are to be billed separately to the payer in accordance with the provisions of the contract with that payer including Medicare.

Medicare pays for the surgical inpatient stay with an inpatient DRG. Other payers pay using various formulas based on the Medicare DRG. To make a margin on surgical inpatient transplant stays, it is necessary to carefully control inpatient resource use. If the cost of the surgical inpatient stay without OACs is less than the amount paid for the inpatient stay, the program will make money on the case. The Medicare DRG payment in Phase 3 excludes any payments for OAC. As such, the financial statement of the transplant program will almost always show a negative

contribution margin and give the false assumption that the hospital is losing money on Medicare cases.

Given that most hospitals focus on the number of transplants as the primary gage for a transplant program's performance, and the fact that the Medicare cost report settlement is reflected on the general ledger of the hospital and not the transplant program's financial statements, the transplant administrator must develop the competency to understand and potentially design the catchment model for all OACs at the CTC. In coordination with the hospital's reimbursement team, the transplant administrator should be able to quantify OAC reimbursement amounts to supplement reporting on DRG payments received for the transplant event in Phase 3.

Medicare pays for the transplant center's post-transplant services under the Ambulatory Payment Classification ("APC") system. Other payers use various formulas, such as a percentage of charges, case rates, etc. To make a margin in the outpatient clinic setting, it is also necessary for the transplant administrator to monitor and control resource use.

It would be a helpful practice for the transplant administrator to team up with the Decision Support department at the hospital to prepare, on a case-by-case basis, a cost analysis of each transplant. The analysis should exclude OACs of any sort and just contain the cost of the inpatient stay and care of the patient. The Medicare DRG, length of stay, and payment amounts could be utilized as a "benchmark" to determine the adequacy of resource utilization. Also, key elements of the surgery can be traced and analyzed.

The primary costs of a transplant case are operating room time, laboratory costs, pharmacy costs, length of stay, and weekend slippage. The weekend slippage is when a patient is medically ready to be released from the hospital after a transplant late on Friday afternoon, but discharge is put off until Monday because of the lack of appropriate staff to release the patient. The transplant administrator should monitor those costs and bring forward a plan to the transplant team to examine better ways to improve the discharge process. Also, utilizing the DRG allows the program to determine if the cost of a Medicare patient is within acceptable norms.

Contract Management

It is not uncommon for hospitals to have contract negotiations held on a system level; that is, services would be negotiated with payers starting from a financial floor established by analyzing the costs of services rendered in the hospital by a certain DRG. It is also not uncommon for the contracting team to not include acquisition costs, or a portion thereof in their negotiations with payers for transplant services, since these are calculated costs at the time of end of the year settlement on the cost report. Some may only settle to include language referring to payment for the cost of acquiring an organ from the organ bank as the only payable amount.

The transplant administrator should host/lead a contracting meeting at regular intervals, where all direct clinical, contracting, billing, and reimbursement staff are invited to share information of current market changes, challenges in billing, or reimbursement and to monitor contract performance. Contract modeling presentations during those meetings would allow for a more robust buy in and education of ways to save money in the course of providing complex and advanced medical and surgical therapies for end-stage organ failure patients at the hospital. It may also trigger discussions among clinicians to focus on alternative protocols to achieve better care and potentially cost savings as well. Most importantly, the transplant providers will be made aware of contract restrictions and would be called upon to participate in negotiations as needed.

Outreach and Program Development

The transplant administrator is responsible for the development of a strategic business and promotional plan(s) for the clinical transplant program. This will include systems for optimizing contribution margin from new and current facility and faculty, identifying funding and personnel for outreach initiatives, and working with marketing and communications to generate an on-going public relations program. Such a program may include, for example, offsite practice development,

creating promotional material, working with existing marketing efforts, consumer seminars, and others.

Conclusion

The success of a transplant program is dependent on the sum of all its parts. As a consultative and procedurally orientated specialty, the transplant administrator plays a critical role to ensure all multidisciplinary team members are properly supported and equally rewarded with adequate budgets and benefits. A transplant administrator can be successful in their role if they comprehend the full demands of the transplant patient care concept, develop a mastery in building a team environment with optimal fiscal management of transplant revenue streams and costs, participate in transplant contract negotiations with payers, and lead efforts for outreach and education.

Cross-References

- ▶ Donor Selection and Operation
- ▶ Intestinal and Multivisceral Transplantation: The Operation
- ▶ Nutrition Considerations in Multivisceral Transplantation
- ▶ Pharmacologic Considerations in Multivisceral Transplantation
- ▶ Psychosocial Issues in Intestinal Transplantation

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Live Donor Intestinal Transplantation

Ivo Tzvetanov, Giuseppe D'Amico, and Enrico Benedetti

Contents

Abstract

Living donor intestinal transplantation (LDIT) has been perfected in relation to technical details, leading to results comparable to those obtained with deceased donors. Because the availability of adequate supply of intestinal deceased grafts, LDIT should be limited to specific indications. In particular, the best indication is probably combined living donor intestinal/liver transplantation (CLDILT) in pediatric recipients with intestinal and hepatic failure. In this setting, the virtual elimination of waiting time may avoid the high mortality currently experienced by candidates on the deceased waiting list. Isolated LDIT may be indicated for candidates to intestinal transplantation with lack of central venous access as a rapid rescue strategy. Potentially, LDIT could be also used in highly sensitized recipients to allow the application of desensitization protocols. Finally, in the specific case of available identical twins or HLA-identical sibling, LDIT has a significant immunological advantage and should be offered.

Keywords

Intestinal failure · Pediatric recipients · Living donor small bowel transplantation · Combined living donor intestinal/liver transplantation

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Introduction

Intestinal failure is defined as a reduction in functioning gut mass below the minimum required for adequate digestion and absorption of nutrient and fluid requirements for maintenance in adults and growth in children (Goulet and Ruemmele 2006). Most cases of intestinal failure are due to loss of the small bowel as a result of surgical resection, and about 10% are due to functional defects of absorption or motility (Ueno and Fukuzawa 2010). In the United States (USA), it has been estimated that about 225,000 patients require enteral or parenteral nutrition (Howard et al. 1995), the cost of which has been estimated to vary from $75,000/- to $250,000/- a year (Sudan 2006).

The existing large gap between the number of potential recipients and available deceased donors for liver and kidney transplant has justified the significant expansion of living donor programs for those organs. This situation does not exist for adult recipients of intestinal transplant as the donor supply largely exceed the current needs. However, this is not the case for pediatric recipients, especially those with associated liver failure.

According to UNOS data, children represent the majority (almost 70%) of the candidates on the intestinal transplantation waiting list in the USA. Most of them are listed for combined liver and bowel transplant. Moreover, UNOS data show that this subset of patients still has the highest mortality rate on the waiting list compared to all the other categories of solid organ transplantation (www.unos.org, SRTR & OPTN Annual Data Report, 2012).

Small bowel transplantation (SBT) provides effective therapy for the patients with chronic, irreversible intestinal failure affected by life-threatening complications of total parenteral nutrition.

Living donor small bowel transplantation (LDIT) potentially can provide advantages, comparing to deceased donor, including better tissue compatibility, shorter cold ischemia time, ability to implement desensitization protocols, and better donor bowel preparation. Probably the biggest advantage is that intestinal transplantation from living donor is an elective procedure, which is done at the optimal time for the recipient.

The outcomes from LDIT in published literature are similar to those from deceased donors, which confirm the viability of the procedure (Testa et al. 2008; Gangemi et al. 2009).

Short Summary of All the Relevant Literature Published

The first clinical transplant from a living donor (LD) was reported in 1971. Alican et al. described the case of an 8-year-old boy with the resection of the small bowel from the ligament of Treitz to the ileocecal valve secondary to strangulation. The transplant was performed with approximately 3 ft. of ileum transplanted from his mother. However, the recipient's procedure was complicated by thrombosis of the vena cava, and the allograft had to be subsequently removed on the ninth post-transplant day (Alican et al. 1971).

The introduction of cyclosporine distinctly changed the outcome for solid organ transplantation. Nonetheless, the use of cyclosporine did not have as much benefit for intestinal transplantation as it did for other transplanted solid organs. In the cyclosporine era, only two intestinal transplants from living donors were reported by Deltz et al. (1990), (Stratta et al. 2012), with both recipients receiving a 60 cm segment of jejunum. First recipient was a boy 4 years of age with volvulus, who received the graft from his mother; unfortunately, the graft was removed due to an intractable rejection episode. Second recipient was a 42-year-old woman with a subtotal small bowel resection secondary to the thrombotic occlusion of mesenteric veins. The patient was on full oral intake 2 weeks later and thereafter remained off parenteral nutrition until 1990, when chronic rejection caused the loss of the graft function. At that point in time, it was the first successful LD intestinal transplant with a long-term function of over 2 years.

The introduction of tacrolimus has allowed intestinal transplantation to become a clinically accepted procedure. Gruessner et al., during the 1990s, studied the technical aspects of LD intestinal transplantation in a pig model (Benedetti

et al. 1995). Consequently, they performed the first LD intestinal transplant (10), from which they concluded:

1. The ileum was the best option due to its greater absorptive capacity of bile acids, vitamins, fat, and water.
2. The terminal ileum (20–30 cm), the ileocecal valve, and the cecum should remain in the donor to minimize morbidity.
3. A vascular pedicle should be used consisting of only one artery and vein (either the ileocolic artery and vein, or the terminal branches of the superior mesentery artery (SMA) and superior mesentery vein (SMV).
4. The bowel continuity should be restored with a proximal bowel anastomosis and a distal ileostomy (to allow access to graft biopsy).

After these two first successful LD intestinal transplants at the University of Minnesota, the group published the respective guidelines in 1997 (Gruessner and Sharp 1997), as a standardized technique for intestinal transplants.

Morris et al., in 1995, described a LD intestinal transplant in an adult patient with a desmoid tumor, whose donor was his monozygotic twin. They transplanted the distal ileum, ileocecal valve and portion of the cecum: however, as they also removed the terminal ileum of the donor, he became Vitamin B12 deficient (Morris et al. 1995).

Uemoto et al. (1998) reported in 1998 the first LD intestinal transplantation in Japan. A 2.5-year-old boy who had been suffering from short bowel syndrome and recurrent line sepsis underwent SBT using a segmental graft from his mother. They resected her distal ilium (100 cm) out of her 460 cm of small intestine. The vessels were anastomosed to the recipient's infrarenal aorta and vena cava, respectively. The donor was discharged on postoperative day 15 without any surgical or medical complication. In 2004, Lee et al. (2004) described the first experience at Catholic University of Korea, Seoul. The patient was a 57-year-old female with short bowel syndrome. A 150 cm distal ileum graft from a 27-year-old living-related donor was successfully transplanted; the graft vessels were anastomosed to the recipient's inferior mesenteric vessels. The donor and recipients recovered without complications.

Ishii et al. (2006), reported in 2006 their experience of two cases of LD intestinal transplantation. The first patients was a 14-year-old boy with TPN-dependent short bowel syndrome associated with hypoganglionosis. The second patient was a 27-year-old female who had undergone massive enterectomy due to volvulus. Up to one third (150 cm in case 1, 210 cm in case 2) of the total small intestine was harvested from the ileum preserving 30 cm of terminal ileum proximal to the ileocecal valve. The vessels were connected to the recipient infrarenal aorta and inferior vena cava. Both donor experienced no complications and were discharged at 10 days after the operation. The two recipients did not have any surgical complications.

Benedetti et al., in 2011, documented their experience with six combined intestinal/liver transplants at the University of Illinois Hospital (Boggi et al. 2012). The transplants were performed between 2004 and 2007, with a total of six children (average age 13.5 months) having received the grafts from one of their parents. Three of these recipients had a simultaneous transplantation, while the other three recipients had a staged procedure, with an average interval of 6 days based on hemodynamic stability after the liver graft was implanted.

None of the donors had any perioperative mortality or morbidity; all donors were discharged home on a regular diet. Five of the six children are still alive with adequate grafts function, whereas one recipient died due to plasmoblastic lymphoma, albeit with functioning graft.

Kumaran et al. in 2012 described the first LDIT in India (Kumaran et al. 2012). The patient required massive bowel resection for gangrene due to thrombosis of the superior mesenteric artery. LDIT was performed using 200 cm of small intestine from the patient's son. The graft was based on the continuation of the superior mesenteric vessels beyond the ileocolic branch. The artery was anastomosed directly to the aorta and the vein to the vena cava.

The graft functioned well and he was weaned off parenteral nutrition. However, he later developed complications (wound dehiscence and enterocutaneous fistula) and developed sepsis. He succumbed to sepsis with a functioning graft 6 weeks after the transplant. The donor recovered uneventfully and was discharged on the fourth postoperative day.

Living donor intestinal transplantation tends to be performed with well HLA-matched grafts. The significance of HLA matching in intestinal transplantation is still to be determined. In fact experienced programs have obtained good outcomes and low rate of rejection with poorly matched deceased intestinal transplantation (Langnas 2004; Reyes et al. 2005).

Garcia-Roca et al. performed two cases of successful LDIT in crossmatch positive recipients (Garcia-Roca et al. 2016). Desensitization protocols were utilized to decrease the levels of alloantibodies and to convert an initial positive crossmatch to prospective donors into a negative crossmatch. No evidence of humoral rejection has occurred in either recipient. Both patients had successful ileostomy reversal at 6 and 9 months, respectively, and are tolerating oral intake.

Donor

The field of solid organ transplantation has realized many technical milestones and functional advances. In the arena of organ procurement, complex medical management of potential deceased donors has increased the number of transplantable organs. During the mid-1980s, transplantation of whole or segmental grafts procured from live donors became a reality. Over the past several decades, few disciplines in surgery have evolved as rapidly with development and application of sophisticated open and minimally invasive techniques as organ harvest from living donors. Furthermore, few areas in medicine have seen such an application of improved techniques and advanced technologies that directly influence long-term patient outcomes in the setting of end-stage organ functions as transplantation.

With the steady expansion of intestinal transplantation (ITx) from deceased donors in the 1990s, liver and kidney transplantation from living donors was also increasingly being employed across North America. Interestingly, ITx from living-related donors had only rarely been attempted (Fortner et al. 1972; Deltz et al. 1989; Morris et al. 1995; Pollard et al. 1996) prior the first report of a standardized surgical approach that was reported by Gruessner and Sharp (1997) from the University of Minnesota in 1997.

In order to minimize the incidence of complications and increase the rate of success, it becomes necessary to choose the donor carefully:

- Comprehensive analysis of medical and surgical history, review of systems, physical examination, current medications, history of malignancy, and previous intestinal surgery
- ABO compatibility, HLAa type, lymphocytotoxic crossmatch
- Comprehensive metabolic panel, vitamin A, D, E, K, and B12
- Prothrombin time, partial thromboplastin time, alpha-fetoprotein, ammonia
- Chest X-ray, electrocardiogram
- Serology (CMV, EBV, VZV, HIV, HCV, HBeAg, HBsAg, HBsAbb), complete blood count. Urine and stool cultures
- Anesthesia history, surgical procedures, and drug allergies
- Psychiatry evaluation, social work consultation
- An interview with a member of the institutional ethics committee to discuss with the potential donor about motivations an understanding of the risk involved
- CT scan of the abdomen or 3D-angio-CT scan

The technical aspects of LDIT were standardized by Gruessner and Sharp in 1997, as was previously described. The authors note the importance of obtaining angiographic images of the superior mesenteric artery pointing specifically the caliber and distribution of the ileocolic artery that will be transected to become the vascular pedicle for the future graft.

Surgical Technique and Postoperative Care

Abdominal cavity is accessed through relatively short (15 cm) midline incision and explored. The entire length of the small bowel from the ligament of Treitz to the ileocecal valve is measured. Subsequently, the cecum and the terminal ileum are identified and marked approximately 30 cm proximal from the ileocecal junction. The donor operation consists of harvesting 200 cm of distal ileum (160 cm for pediatric recipients), preserving at least 20 to 30 cm of terminal ileum and ileocecal valve to avoid macrocytic anemia and to shorten transit time. The vascular pedicle of the graft is formed by the ileocolic artery and vein. This vessels will be anastomosed to the infrarenal aorta and vena cava of the recipient, respectively.

If the procedure involved a combined intestinal and liver transplant, the donor operation becomes more complex. Combined living donor intestinal and liver transplants have only been done for pediatric patients. If the recipient remains stable after the liver is implanted, the intestinal procurement (and consequently the transplant) can be performed; otherwise, the incision is closed and the intestinal transplant is rescheduled, preferably within the two first weeks after the liver transplant.

It is very important that the donors have adequate follow-up care. After discharge they need to be evaluated on a monthly basis and then annually to review their nutritional and bowel habits as well as any complications. The donor should also undergo vitamin B12 assays at 1, 6, and 12 months post donation to ensure adequate vitamin B12 absorption.

Benedetti et al. reported a case of chronic diarrhea among their donors, but it was resolved with medical therapy consisting of Imodium and cholestyramine (Boggi et al. 2012). For 11 donors, out of their total cohort of LD intestinal transplants at the University of Illinois, the authors also reported a 36.4% reduction in LDL and a 22.3% decrease in total cholesterol levels when compared with their respective pre-donation lipid profiles, and they noted that the difference was statistically significant (Ghafari et al. 2012). However, a further follow up in a greater cohort should be completed to conclude this finding.

Although the number of LD intestinal transplants is relatively small, there have been no reports of donor mortality or life-threatening complications (Gruessner and Benedetti 2008). Nevertheless, a more extensive follow up is necessary to determine the presence of postsurgical complications, such as intestinal adhesions.

Recipient

Graft and patients survival improved over the past decade. The graft failure rate among intestine transplant recipients was 17.3% at 6 months for transplants in 2013, 23.2% at 1 year for transplants in 2013, 45.3% at 3 years for transplants in 2009–2010, 49.5% at 5 years for transplants in 2007–2008, and 66.3% at 10 years for transplants in 2003–2004.

For intestine transplants with or without a liver in 2009, 1- and 5-year graft survival was 69.1% and 49.2%, respectively, for recipients aged younger than 18 years, and 65.1% and 42.5%, respectively, for recipients aged 18 years or older. One- and 5-year graft survival was 66.2% and 44.1%, respectively, for recipients of intestines without a liver, and 65.9% and 48.1%, respectively, for intestine-liver recipients. Pediatric and adult patient survival was superior for intestine recipients compared with intestine-liver recipients. Patient survival was lowest for adult intestine-liver recipients (1- and 5-year survival 61.6% and 37.2%, respectively) and highest for pediatric intestine recipients (1- and 5-year survival 89.8% and 74.6%, respectively). (www.unos.org, SRTR & OPTN Annual Data Report, 2014).

Registry data suggest that the patient and graft survival rates are similar for both LD and DD intestinal transplants. Nevertheless, using a living donor can reduce the mortality rate for those on the waiting list, which is especially high for candidates less than 5 years of age (www.unos.org, SRTR & OPTN Annual Data Report, 2012).

About 15% of patients receiving TPN for more than 1 year develops end-stage liver disease. In children the incidences of liver disease is higher,

especially in patients with less than 30–40 cm of remnant bowel (Kelly 1998). Liver disease remains the leading indication for performing intestinal transplantation in children, but loss of central venous access to provide parenteral nutrition has become an indication for intestinal transplantation.

The indications for intestinal transplantation in pediatric patients were updated in 2010 by Avitzur and Grant (Halme et al. 1997):

- Loss of 50% of available central venous accesses due to thrombosis
- Recurrent septic episodes, resulting in multiorgan failure, shock, and metastatic infectious loci (more than two episodes per year)
- Imminent or overt end-stage liver disease
- Ultrashort bowel syndrome
- High risk of death attributable to the underlying disease
- Frequent hospitalization
- Severe dehydration episodes
- Lack of family support or unwillingness to accept long-term TPN

A multidisciplinary evaluation of the patient with intestinal failure is essential to assess adequate candidacy for transplantation and to ensure best outcomes. The evaluation process must elucidate: (1) the failure of TPN as compared to other surgical therapy strategies besides transplantation, (2) the need of intestine or combined liver/intestine transplantation, (3) the state of the remnant intestine and the patency great vessels, (4) and the absence of absolute contraindications or associated disease that can put at risk the procedure and postoperative course. All the aspects of the recipient evaluation are summarized as follows:

- Comprehensive analysis of medical and surgical history, review of systems, physical examination, current medications, current nutrition requirements
- Blood group, HLAa type, panel of reactive antibody
- Upper and lower gastrointestinal barium study, esophagogastroduodenoscopy and colonoscopy, CT scan abdomen and pelvis, motility studies (if indicated)
- Height, weight, anthropometric measurements, nutritional support, comprehensive metabolic panel, zinc
- Prothrombin time, partial thromboplastin time, alpha-fetoprotein, ammonia. Doppler ultrasound of liver and liver biopsy (if indicated)
- Electrocardiogram, chest X-ray, echocardiogram, stress test if more than 50 years of age or with cardiac history, and risk factors (hypertension, diabetes mellitus)
- Abdominal ultrasound with size of kidneys, triple renal scan, 24 h creatinine clearance
- Doppler ultrasound of upper and lower extremities veins
- History of infection episodes, immunization, serology (CMV, EBV, VZV, HIV, HCV, HBeAg, HBsAg, HBsAbb, measles, rubella and mumps titers), complete blood count. Blood, urine, and stool culture
- Anesthesia history, surgical procedures, and drug allergies
- Child life and development
- Psychiatry evaluation, social work consultation
- Doppler ultrasound of great vessels and angiography or MRI or 3D-angio-CT scan (if indicated)

Although the criteria used for listing deceased and living donor candidates are the same, certain patients may have a greater benefit from the living donor option. Adults with an identical twin or HLA-identical sibling as a donor candidate should be transplanted without delay. Using donors with at least one haplotype match has been extremely favorable, with no acute rejection episodes during the first year post-transplant. In children affected by ultrashort bowel syndrome with slim possibilities of successful weaning of TPN, LD intestinal transplant should be considered early in order to avoid progression to end-stage liver disease. For children who present TPN-related cirrhosis, the option of combined liver-bowel transplant from an adult donor may contribute to minimize the probability of death on the waiting list, which is extremely high in this population.

Surgical Technique and Postoperative Care

A midline incision is made. After the remaining small bowel is mobilized, the infrarenal aorta and vena cava are identified and dissected free from the point of takeoff of the renal vessels to their bifurcations. The arterial anastomosis is done first, since it is more technically challenging due to the small diameter of donor's artery. The arteriotomy of the anterior wall of the aorta is made at the level between the origins of the inferior mesenteric artery and the renal arteries. Given the small size of the ileocolic artery of the graft, the end-to-side ileocolic artery-to-infrarenal aorta anastomosis is constructed in an interrupted fashion. Continuing with the venous anastomosis, an appropriate site on vena cava is chosen for the venotomy, usually 2–3 cm proximal to the arterial anastomosis. The venous anastomosis is done with the quadrangulation technique, and the end-to-side ileocolic vein to infrarenal cava anastomosis is completed by continuous suture. The proximal end of the intestinal graft is anastomosed to the remaining recipient duodenum/jejunum. This anastomosis could be made in an end-to-end, end-to-side, or side-to-side fashion, using hand-sewn or stapled techniques. The hand-sewn technique decreases the risk of intraluminal anastomotic bleeding, as compared to stapled anastomosis.

Except with identical twins, the distal end of the donor graft should be brought out as a stoma to allow an easy access to endoscopy and biopsy. The first 24–48 h are crucial due to surgical trauma, the degree of ischemia and reperfusion injury, and onset of immunosuppression. Initially, vital signs, color of the ostomy, and laboratory parameters are monitored every 4 h. An important element to immediately monitor post-transplant is systemic anticoagulation: due to the small diameter of the ileocolic vessels of the LD graft, they are more prone to vascular thrombosis. On post-transplant day seven, a small bowel follow-through contrast study is performed to confirm intactness of the anastomosis; and, on the next day, the first graft biopsy is to be done. After an anastomotic leak is ruled out, recipients begin a clear liquid diet. For recipients of a combined LD liver and intestinal transplant, postoperative care is initially dictated by the liver graft function. Once liver function has stabilized, the attention can be directed to the intestinal graft function.

The immunosuppression and follow up of LDIT recipient does not differ significantly from DD recipients.

Current Status of Intestine Transplantation

According to United Network for Organ Sharing (UNOS) data, the total number of registrations on the intestine waiting list in 2014 is 261, where 54.2% of the candidates are under 18 years of age. The proportion of newly listed patients who were 18 years of age or older had been increasing in the prior decade. However, the number of patients on the waiting list under 18 years of age remained higher as compared who were 18 years of age or older, especially for those patients under 5 years of age (71.4% and 51.8%, respectively) (www.unos.org, 2014). This data further indicates that pediatric patients have a higher risk of life-threating complications secondary to TPN, when compared with adults.

During the last decade, the number of intestinal transplants increased more than twofold. In 2009, there was a total of 180 intestinal transplants, of which 94 (52%) were for recipients less than eighteen (18) years of age. This increase was due primarily to a higher number of isolated intestine transplants as well as to increased number of combined liver/intestine transplants. Through the same year, 89 (49.4%) recipients required a combined liver and intestinal transplants (www.unos.org, SRTR & OPTN Annual Data Report, 2012). Children are the primary candidates for intestinal transplantation, and more than 70% are affected by intestinal and liver failure. Recipients of a combined graft experience better graft survival outcomes compared to those who received an isolated intestinal transplant (Testa et al. 2008; Gangemi et al. 2009).

According to UNOS, between 1990 and 2013, the rate of DD intestinal transplants had increased from 0.2% to 4.3%. However, the rate of LD intestinal transplants remains very low, with only 1 transplant performed in 2013. The total number of LD intestinal transplants in the USA is 40, 26 of which are performed by the team at The University of Illinois at Chicago where the longest living donor intestinal graft survival is 15 years (unpublished data). Current data indicates that the 5-year patient survival probability was superior for LD intestinal transplant recipients as compared to intestinal/stomach and deceased intestinal transplant recipients (2011 Intestinal Transplant Registry Report, www.intestinetransplant.org). However, the experience with LD intestinal transplants remains limited, with a very small number of procedures having been performed worldwide.

Between 1998 and March 2016, a total of 33 living-related donor bowel transplants were performed at the University of Illinois at Chicago. The 1,5, and 10 year patient survival was 90%, 80%, and 70%, respectively. The graft survival was 80%, 60%, and 60%, respectively. Among ten pediatric recipients, four with isolated living donor intestinal transplant and six with combined living donor liver/intestine transplant, the 1, 5, and 10 years patient survival of 90%, 80%, and 70% and graft survival of 80%, 60%, and 60%, respectively.

Seven children are currently alive with perfectly functioning graft, oral diet without any requirement for TPN (6 with over 10 years of follow-up and the other with 3 years of follow-up). Six children are currently enrolled in school and one child is homeschooled. All children report good quality of life with great adaptation to daily. Their related donor and all their families report great satisfaction with their accomplishments.

Conclusion

LD intestinal transplantation has been perfected relative to technical details, leading to results comparable with those achieved with deceased donor transplants. However, LD intestinal transplantation should be limited in accordance with specific indications. In particular, the best indication is probably for combined LD liver and intestinal transplantation in potential pediatric recipients with an intestinal and hepatic failure. For these potential recipients, the virtual elimination of waiting time may diminish the potential of high mortality associated with the waiting list. Isolated LD intestinal transplantation may further be indicated for candidates in need of an intestinal transplant with lack of central venous access as a rapid rescue strategy. Potentially, LD intestinal transplantation could be used with highly sensitized recipients, to allow the application of desensitization protocols. Finally, in the specific case of available identical twins or HLA-identical sibling, LD intestinal transplantation has a significant immunological advantage and should be offered.

Cross-References

- ▶ Intestinal and Multivisceral Transplantation: The Operation
- ▶ Pathology of Intestinal Transplantation
- ▶ Pharmacologic Considerations in Multivisceral Transplantation

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Psychosocial Issues in Intestinal Transplantation

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Contents

Abstract

The role of psychologist with patients referred for intestinal transplantation is both evaluative and supportive. Transplant candidates are interviewed to ascertain their mental and behavioral capacity to succeed in the transplant situation. Areas reviewed include cognitive function, adherence, psychopathology, substance use, and social support. Where deficits are identified, efforts are made at remediation or compensation. After transplantation, psychological support can help with psychopathology, coping, and quality of life. Future directions include an appreciation for how pre-transplant and posttransplant gut biomes may modulate psychological function.

Keywords

Intestinal transplantation · Organ transplantation · Abdominal organ transplantation · Multivisceral transplantation ·

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Introduction

The psychological situation of intestine transplantation (IT) patients is typically of long suffering and multiple failed interventions culminating in a referral for transplantation. Until about 10 years ago, IT was a last choice as survival rates were low and the procedure was seen as unlikely to provide quality of life superior to other treatment strategies. With advances in immunosuppression and earlier referrals, IT is now seen as a way to gain freedom from intravenous nutrition, achieve gut autonomy, and decrease health interference in daily functioning. Although a significant number of people post-IT will enjoy these benefits, there is often an extended recovery period of intensive management of expected complications, and full restoration of social/emotional equilibrium is not often achieved. The nearest horizons for advancement in IT will address posttransplantation complexities, including a more sophisticated appreciation of the role of the gut biome in overall health and functioning.

IT Patient Experience

At the time of referral for IT, patients and their families are often experiencing multiple sources of stress. The medical evaluation for listing suitability usually occurs in the context of advancing disease and disability (Barbour et al. 2006), resulting in loss of capacity to engage in or perform previous responsibilities and/or pleasures. The workup process can be expensive in terms of both time and money. If the transplant center is far from home, stressors can include relocation, loss of social support, job loss, and the like (Sorrell 2008). People who seek transplantation may worry about the burden of their illness and incapacity on others while facing their own mortality concerns (De Oliveira et al. 2014). Patients are aware that not enough organs are available to transplant all who need grafts, raising concerns that they will be denied by a committee that is tasked with making judgments of maximal benefit (Ehlers 2008).

Adult referral for intestine transplantation is often made after years of coping with chronic, painful disease and multiple surgical resections resulting in gut failure and reliance on parenteral nutrition (Abu-Elmagd 2015; Kubal et al. 2015) . Even when the indication is acute, it is the compromise of nutrition and hydration that drives referrals for IT (Kubal et al. 2015). In children, the referral is often within the first few months of life for short gut syndrome (gastroschisis, necrotizing enterocolitis, or volvulus) or motility disorders (Boluda 2015). Facing IT is stressful for patients and their families because of the mix of promise and threat inherent in the procedure. There is awareness that transplant is offered only for life-threatening conditions and it also poses new risks.

Pre-transplantation Psychosocial Evaluation

Careful selection of and preparation of patients prior to listing for transplantation is believed to reduce morbidity and mortality. In addition to medical evaluations and educational programs, a psychosocial evaluation is typically conducted to assess known risk factors including capacity for medical adherence, psychopathology (including substance use disorders), adequacy of social supports, and cognitive function (Kuntz et al. 2015; Dew et al. 2000). Appraisal of patients and families' resources and needs is critical in early stages of the IT workup to maximize chances of success (Stenn et al. 1992; DiMartini et al. 1996).

Psychosocial considerations specific to intestine transplantation candidates can include the scarcity of IT centers, lengthy postoperative hospital stay and follow-up, and increased

complication rates (especially when a multivisceral transplant is performed). Although psychometric devices have been developed to aid in the assessment of transplant candidates (Twillman et al. 1993; Olbrisch and Levenson 1995; Maldonado et al. 2015), the psychological/psychosocial evaluation is not standardized among transplant centers. Nevertheless, most will include the essential domains discussed in following sections.

Cognitive Function

Capacity to understand one's medical situation, including the vicissitudes of transplantation, is necessary for informed consent (Levenson and Ellen 2000). Illness, age, malnutrition, and injury can compromise cognition, thereby impeding patients' ability to take in education about their treatment options. When too young or impaired to decide for themselves, patients' advocates, guardians, or parents will decide and will be asked to commit to providing ongoing support after transplantation. With social support that provides material assistance (including medication administration), developmental delays and psychotic disorders have been shown to not contribute to negative transplant outcomes (Martens et al. 2006; Zimbrean and Emre 2015). Limitations of intelligence and literacy are similarly managed with robust support commitments and not considered absolute contraindications.

Adherence

Posttransplant compliance with routines of self-care and medical management are predicted by interviewing patients/family and reviewing current and past medical records (Heinrich and Marcangelo 2009). Prior to transplant listing, patients undergo extensive testing and have multiple appointments; the ability to successfully attend these while maintaining appropriate self-management routines (e.g., medication administration, diet adherence, etc.) is seen as indicative of capacity to perform similar tasks after transplantation (Lieber and Volk 2013). Patients referred for transplant who have a history of poor compliance with medical care are typically required to establish a period of cooperation with defined behaviors set out in a written contract in order to advance toward listing (Cupples and Steslow 2001).

Medication adherence is a signal concern for transplant teams because failure to administer immunosuppressant medications properly is a prominent cause of graft failure in transplantation of all solid organs (Denhaerynck et al. 2005; Dew et al. 2007). Currently, most IT recipients take tacrolimus twice daily and have frequent clinic visits to ensure that dosages are sufficient to avoid rejection. This regimen can become burdensome to recipients, leading to nonadherence. A 2005 review of 38 studies on medication compliance in the kidney transplant population showed nonadherence in 20% of late acute rejection episodes and 16% of graft failures (Denhaerynck et al. 2005). Noncompliance among liver transplant patients has been estimated at about 15% (O'Carroll et al. 2006; Berlakovich et al. 2000). Even when not associated with rejection episodes, up to 68% of transplant recipients are seen as failing to dose their antirejection medications appropriately (Dew et al. 2007).

Psychological factors including anger, depression, and hostility have been associated with poor adherence (Dew et al. 1999). Personality features that interfere with forming a cooperative and trusting relationship with the transplant team (e.g., narcissism, sociopathy) have also been suggested as impediments to proper self-care after transplantation (Kuntz et al. 2015). On the other hand, higher levels of conscientiousness prior to transplant and practical support from others are both associated with better adherence after transplantation (Fineberg et al. 2016; DiMatteo 2004). Thus, functioning of candidates and their support systems is carefully gauged in the psychosocial evaluation.

Psychopathology

Studies on psychopathology in the IT population are few but seem to point to a prevalence of

psychological symptoms both before and after transplantation, likely as a result of chronic illness and the rigors of the transplant process. DiMartini and associates reported that 63% of the adult IT patients at their facility required psychiatric intervention during the transplant process (DiMartini et al. 1996). Another investigation found that 68% of IT patients had diagnosed mental health disorders before surgery, with most identified as depressed (56%) (Pither et al. 2014). The same study found marked increase in mental health problems after transplant: fully 88% had a psychiatric diagnosis after transplantation (mostly depressive disorders). Even before referral for IT, people with inflammatory bowel disease (a condition that can lead to referral for IT) are more prone to depression and anxiety after diagnosis with their condition (Kurina et al. 2001).

Interference in patient functioning caused by mood or other psychiatric illness can warrant referral for psychotropic medication and/or psychotherapy if the impairment appears likely to disrupt medical care or self-care (Kuntz et al. 2015; Heinrich and Marcangelo 2009). Active suicidality and untreated psychosis are likely to be seen as absolute contraindications for listing. Occasionally, referred patients are simultaneously undergoing psychological treatment. Any current mental health providers may be requested to provide the transplant psychologist with updates regarding patient progress. Patients may then undergo a subsequent interview with the transplant psychologist to assess readiness and capacity for intestine transplantation.

Psychometrics may be used to provide additional assessment of patients' psychological status. Measurement devices with which psychologists are typically familiar include the Beck Depression Inventory-II (Beck et al. 1996), the Minnesota Multiphasic Personality Inventory – 2 – Restructured Form (Ben-Porath and Tellegen 2008), the Hospital Anxiety and Depression Scale (Snaith and Zigmond 1986), and the Patient Health Questionnaire (Spitzer et al. 1999). Transplant-specific rating scales have been developed including the Transplant Evaluation and Rating Scale (Twillman et al. 1993) and the Stanford Integrated Psychosocial Assessment for Transplantation (Maldonado et al. 2012). Assessment measures are not used in lieu of a full psychological evaluation but as additional data sources.

Literature on treatment of psychopathology prior to organ transplantation indicates that identification and treatment of disorders prior to surgery is seen as increasing the likelihood of graft and patient survival (Surman et al. 2009; Dew et al. 2015). For instance, the presence of depression in liver transplant recipients was associated with poorer quality of life after transplant as well as continued depression and even suicidal ideation (Fineberg et al. 2016). For heart or lung recipients, pre-transplant psychopathology was among a set of identified risk factors for posttransplantation psychiatric disorders (Dew et al. 2012). A more targeted literature review conducted by Davydow showed that presence of psychopathology pre-transplant was strongly associated with the development with post-traumatic disorder after transplant (Davydow et al. 2015).

Although vigilance for and aggressive treatment of pre-transplantation psychopathology is urged (Pither et al. 2014; Sorrell 2008), oral psychoactive medication absorption can be limited in gut failure (Crone and Gabriel 2004; Sorrell 2008). Several strategies for the use of antidepressants have been suggested by Sorrell: mirtazapine can be administered in an orally dissolvable form, possibly increasing chances of usefulness; nortriptyline has a therapeutic window which can be monitored via blood levels providing an objective indicator of action; and a transdermal monoamine oxidase inhibitor (selegiline) could be useful in bypassing enteral absorption altogether (Sorrell 2008).

In general populations, psychotherapy has repeatedly shown effectiveness in improving mood, coping, and functional behavior. Research on positive adaptation to chronic illness points to the utility of encouraging patients to remain as active as possible, to manage behavior, to express emotion, and to cultivate optimism (de Ridder et al. 2008). In organ transplantation populations, counseling has been shown to improve mood, intimate communication, and quality of life (Rodrigue et al. 2005). Specific interventions, such as mindfulness training, have been shown to improve

mood, sleep, and quality of life (Gross et al. 2010). In pediatric populations, problem-solving therapy for parents has shown benefit (Law et al. 2014). Specific to IT patients, there is empirical evidence that focusing psychotherapy on increasing action-oriented coping strategies is helpful in patients' adaptation to the often long course of treatment and recovery (Golfieri et al. 2007). Researchers in this area have proposed that foci for psychotherapy differ between the stages of transplantation: pre-transplant listing, waiting for transplant, and postsurgery (Rainer et al. 2010).

Substance Use/Abuse/Dependence

Assessment of substance use is based on a comprehensive interview of the patient, usually with a close family member or other support person (s) present to provide additional information. Areas assessed include types of substances used, duration and intensity of use, life interference from use, attempts to limit or stop use, recovery strategies, and commitment to abstinence. Most transplant programs require a defined period of abstinence, but there is variability in duration. Transplant centers may insist on successful completion of a substance abuse treatment program if the substance is deemed especially problematic (e.g., alcohol for liver transplant recipients, cigarettes for lung transplant recipients) or if the pattern of use is deemed pathological.

Treatment for substance use disorders begins with an assessment of whether the individual is at risk for withdrawal symptoms (Parker et al. 2013). Referral to outpatient relapse prevention programs is common and widely believed to provide patients with the skills needed to build a recovery program and resist future urges to relapse. Recent data indicate that such behavioral treatments may be most successful in reducing relapse if required both before and after transplantation (Rodrigue et al. 2013). Other forms of treatment include support group attendance (e.g., Alcoholics Anonymous, Narcotics Anonymous), inpatient treatment, and aftercare programs (Gentleman et al. 2008). Random urine and blood screens can be used to verify abstinence.

Alcohol

Malabsorption and avoidance of oral intake may account for the lack of empirical investigations of alcohol use disorders in the IT population. Persons referred for IT suffer intestinal failure and are dependent on parenteral nutrition, sometimes not even drinking water. Occasionally, cases of alcohol use disorders are seen in persons referred for IT due to acute abdominal trauma or necrotizing pancreatitis. Studies of alcohol use in the transplantation population are almost exclusively conducted for persons with liver disease (Dew et al. 2008). Results of these studies are probably generalizable to all solid organ transplants but particularly relevant for persons with combined liver/intestine or MVT grafts.

Consideration of patients' alcohol use is routine in all pre-listing psychological evaluations and contributes a valuable insight into patients' functional capacities. Predictions of patient welfare can be influenced by which type of medical professional diagnoses an alcohol use disorder. This effect was brought to light in the liver transplant population when outcomes were compared after either a mental health provider or a medical provider diagnosed the alcohol problem. Outcomes after liver transplantation for *gastroenterologist-diagnosed* alcoholic liver disease were not different from outcomes after transplantation for other causes of end-stage liver disease (Murray et al. 2005). This result encouraged conclusions that transplantation for alcoholic liver disease is a reasonable use of a limited resource. However, Rowley and colleagues showed significant reduction in survival for persons with *psychiatric diagnoses* of alcohol dependence or abuse (Rowley et al. 2010). They argue that the constellation of maladaptive behaviors associated with psychiatrically defined substance use disorders is significantly more disruptive to overall functioning than is medically defined alcohol liver damage.

When an alcohol use disorder is identified, most transplant programs require 6 months abstinence and behavioral/psychological treatments prior to listing for transplantation (Leong and Im 2012). The consensus for "the 6-month rule" is partly based on assumptions that this period allows for drug and alcohol testing to support

claims of abstinence and allows the transplant team a period of time to assess patients' commitment to the rigors of transplantation. In cases of identified alcohol use disorders without significant compromise of the liver, metadoxine, acamprosate, and baclofen are sometimes added to a behavioral regimen to increase chances of alcohol abstinence (Borro et al. 2016).

After transplantation, some level of alcohol consumption is common, even for liver transplant recipients. In their review of 54 studies, Dew and colleagues calculated an annual return to any drinking of 5.6% and relapse to heavy use at 2.5% per year (Dew et al. 2008). They noted small but significant correlations between relapse and poorer social support, family history of disordered alcohol use, and shorter duration of sobriety prior to transplantation (6 months or less). They did not find consistent support for the notion that relapse is associated with nonadherence. Nevertheless, most programs ask patients to permanently abstain from alcohol use (Heinrich and Marcangelo 2009).

Cannabis

Cannabis use by patients is a challenging issue for transplant programs. In a 2013 accounting, it was the most commonly used illegal drug in the world, used by 12% of Americans over the age of 12 (Center for behavioral health statistics and quality. National survey on drug use and health, Rockville, MD: Substance abuse and mental health services administration; 2013). Medical uses are debated and only a few indications validated empirically. Studies have shown that marijuana can help with sleep, appetite, and pain (Grant and Cahn 2005; Lynch and Campbell 2011; Zajicek et al. 2012), but adverse lung (Tashkin 2013) and vascular effects (Thomas et al. 2014) have also been identified. Psychological complications from cannabis use can include cognitive impairment (Meier et al. 2012), psychotic symptoms (Moore et al. 2007; Zammit et al. 2002; Henquet et al. 2005), anxiety (Zvolensky et al. 2006), and depression (Bovasso 2001).

Cannabis is an intoxicant that many transplant centers view with uncertainty regarding behavioral and medical interference (Coffman 2008). Adherence concerns drive much of the debate about marijuana use in transplant recipients, but no empirical investigations have definitively linked the two. Much as with the issue of alcohol use, it is likely that diagnosis of a cannabis use disorder by a mental health professional warrants attention as this diagnosis would point to a constellation of maladaptive behaviors which may well interfere in appropriate adaptation to the transplant situation. Recent attention has focused on reports of cannabis-associated variations in immunosuppressant levels (Iwasaki 2007; Hauser et al. 2016), but no clear conclusions are reached. To date, the most relevant evaluation of marijuana effects on patients after transplant (kidney) was conducted by Greenan and associates (Greenan et al. 2016). They reviewed 1225 cases and concluded that marijuana use "is not associated with poorer patient or kidney allograft outcomes at 1 year," recommending that recreational marijuana use is no longer be considered a contraindication to transplantation.

Cannabis use presents challenges to transplant teams because of its relative ubiquity contrasted with its mostly illegal status. In a recent national survey, 7.8% of US adults described using marijuana in the previous month (Azofeifa et al. 2016). The same survey found that 44% of persons aged 12 or older had ever used cannabis in their lifetime, identifying marijuana as the most frequently used illegal substance. National trends toward legalization of cannabis, for both medical and recreational use, are progressing but remain far from complete. As of this writing, 28 states (plus Guam and the District of Columbia) allow medical use; seven states and the District of Columbia allow recreational use; and eight states have passed laws that forbid transplant centers from denying patients on the basis of medical marijuana use.

There is wide variation in marijuana policies at transplant centers in the United States (Neyer et al. 2016). Even in states with laws prohibiting denial of transplant to persons who use medical marijuana, most respondents in the Neyer survey reported that their center either denied users from listing or required abstinence prior to listing.

As Allen and Ambardekar point out in their discussion of the Neyer study, "There were no differences between the proportion of respondents supporting transplant listing after stratification by profession or region, suggesting that this heterogeneity reflects individual opinion rather than regional legal or cultural norms"(Allen and Ambardekar 2016). With wider legalization comes greater freedom to research cannabis effects in the transplantation population. Transplant programs will need to consider results of these studies as they advise patients regarding safety and acceptability of marijuana use.

Tobacco

Tobacco use is a known cause of disease and dysfunction in many organ systems including cardiovascular, vascular, gastric, pulmonary, and cerebral. In the transplant community, concerns about surgical healing (Silverstein 1992) and increased recipient mortality (Leithead et al. 2008) contribute to policies requiring abstinence from tobacco. However, as with cannabis, there is variability among centers such that 44% have no absolute policy for abdominal organ recipients (Cote et al. 2016). On the other hand, heart and lung transplant programs are far more likely to demand tobacco abstinence (Mehra et al. 2016). The lack of absolute contraindication at some centers may be based on considerations of fairness given that less education and lower socioeconomic status are associated with higher rates of smoking (Reid et al. 2010). Published accounts of the frequency of refusal to list current tobacco users are not available for the IT population, but it is likely that these programs also encourage cessation prior to listing and may demand cessation in persons who are deemed to already have end organ disease caused by smoking or chewing tobacco.

When requiring cessation, transplant centers may try to direct patients' quitting attempts. In their review, Corbett et al. (Corbett et al. 2012) summarize studies of cessation therapies with encouraging results, especially for combined nicotine replacement and psychotherapy. They point out that smoking can be considered a behavioral contraindication for transplantation much like excessive alcohol use or nonadherence to immunosuppressive regimens: all can damage the graft and decrease survival rates, prompting considerations of allocation according to maximal benefit.

Opioids

Many intestine failure patients are maintained on high doses of narcotics because most of the indications for IT are for chronically painful conditions such as pseudo-obstruction, short gut syndrome, and Crohn's disease (DiMartini et al. 1996). Frequently, physical discomfort is accompanied by psychological distress due to fears of disease progression, anticipated future interventions, and feelings of lost control (Sorrell 2008). Consequently, many IT candidates also take anxiolytic and/or antidepressant medications.

Addiction to narcotics in the IT population can be difficult to identify because of patients' frequent histories of chronic pain requiring long-term opioid medication use. In population studies of chronic pain sufferers, use of opioids is seen as less likely to be driven by cravings or interpersonal stressors when compared to cohorts without chronic pain (Weiss et al. 2014). Making matters more complex is that definitions of aberrant use differ between diagnostic strategies: International Classification of Diseases vs Diagnostic and Statistical Manual vs pain medication specialists (Campbell et al. 2016). Many prescribers identify problematic use of narcotics through the observation of six factors outlined by Trescot and associates: excessive narcotic needs, deception to obtain narcotics, "doctor shopping," poor functional status, exaggerated pain complaints, and forgery of prescriptions (Trescot et al. 2006). Fortunately, efforts to manage pain effectively in noncancer patient populations are aided by guidelines published by the American Society of Interventional Pain Physicians (Manchikanti et al. 2012a, b).

Pre-transplant use of narcotics is associated with posttransplant complications including increased mortality and graft loss in kidney and liver recipients (Weinrieb et al. 2004; Lentine et al. 2015). There is an effort to wean patients as much as possible before transplant through carefully monitored dose reductions, sometimes including substitution therapies with methadone

and buprenorphine (Connock et al. 2007; Rodgman and Pletsch 2012) or medical marijuana (Meng et al. 2016). For chronic pain patients with a known history of opioid addiction, treatment options are more complex although newer opioid agonist therapies show promise (Dennis et al. 2015). Behavioral treatments such as psychotherapy, chemical dependency treatment programs, and support group attendance can improve coping with emotional distress, further decreasing the need for potentially addictive psychopharmacological agents. After transplantation, pain management strategies must account for presurgical narcotic use and often continue medications for mood control (Siniscalchi et al. 2002). Observations of supplementation of prescribed narcotics with illicit substances have been reported for the IT population (DiMartini et al. 1996), prompting vigilance in providers. Ongoing monitoring of opioid use (sometimes with the aid of assessment devices such as the Opioid-Related Behaviours In Treatment scale) helps to minimize unintended negative consequences such as diversion, addiction, and death (Larance et al. 2016).

Social Support

Transplant candidates need help from dedicated caregivers, typically family or close friends, especially in the first months after transplant (Levenson and Ellen 2000; Gentleman et al. 2008). Compared to other abdominal organ transplants, IT recipients require a longer stay in the hospital and residence close to the hospital after transplantation, often for many months. Because IT programs are the least common in the USA (Sudan 2014), travel to a transplant center is often necessary, adding stresses on support systems. Relocation to an IT center can result in disruption of caregivers' ability to work, to provide care for other family members, and to receive support themselves; the cost of relocation/travel can be a burden, as can simply learning a new locale (Gentleman et al. 2008).

Psychologists on staff with transplant programs can be helpful to patients and their support providers through counseling regarding the extent and anticipated changes in role functions before and after surgery. Social workers are especially skilled at working on issues related to finances, travel, lodging, and medical insurance. Many centers offer support groups where patients and their support people meet with others who are tackling similar challenges to exchange information, providing for another type of community.

Special Considerations with Pediatric Populations

Pre-transplant psychosocial evaluations of children and their families are used to identify areas of need for services or support to bolster readiness for surgery (Annunziato et al. 2010; Gentleman et al. 2008). Parental/caregiver capacity for medication management of the child is reviewed because of associations between pre- and posttransplant medication management (Stone et al. 2006; Dobbels et al. 2009). Patients and families are evaluated for their knowledge about transplant, and assessments are made of neurocognitive, psychological, and family functioning (Lefkowitz et al. 2014). Research has indicated that children with psychopathology and family dysfunction before transplantation suffer more medical complications afterward (Annunziato et al. 2012). Psychological and family dysfunctions are not usually absolute contraindications for transplantation but rather conditions that warrant referral for psychological treatment (Lefkowitz et al. 2014). Neurodevelopmental delay is similarly not always seen as an absolute contraindication to organ transplantation, but it is considered carefully at many centers as they weigh expected benefit from the procedure (Richards et al. 2009).

Successful transitioning to adult care for the patient transplanted as a child minimally requires understanding of the need for transplantation, mastery of the medical regimen, and the ability to perform self-care routines independently (Bell et al. 2008). Unfortunately, teens and young adults have higher rates of graft loss and death than do either adults or children (Watson 2000; Van Arendonk et al. 2014; Annunziato et al. 2007). Adherence to medication administration has been identified as one factor contributing to this

problem (Akchurin et al. 2014; Simons and Blount 2007) and age-adapted solutions such as cell phone applications are being explored (Lefkowitz and Fitzgerald 2016; Shellmer et al. 2016). Evidence suggests that a gradual transitioning of responsibility for self-care and extensive education of both parents and teens can increase the likelihood of post-transfer adherence in adolescents (Fredericks et al. 2015).

Posttransplantation Adaptation

After intestine transplantation patients are faced with adjustment to new routines of self-care and new forms of medical management. Focus shifts from efforts at stabilization to that of recovery, with the foremost goal of nutritional autonomy. The main medical tasks in early weeks are infection control, immunosuppression adjustment, graft monitoring, and diet advancement. Postoperative medical care includes an expectation that bacterial infection will occur (Mangus et al. 2013). Other complications can include lymphoproliferative disease, graft versus host disease, chronic rejection, and chronic kidney disease. The typical hospital stay after transplantation is about a month followed by intensive outpatient monitoring for a number of months. Survival rates have improved in recent years (Smith et al. 2015) with adult 1-year graft survival at 90% (O'Keefe and Matarese 2006) and up to 61% after 15 years (Abu-Elmagd et al. 2012).

Psychological Adjustment

Patients' adjust to novel arrangements for chronic conditions is typically successful. Education regarding usual posttransplantation routines can aid acceptance and planning, as well as reduce emotional distress associated with necessary changes. Recipients are instructed that accurate medication administration, regular laboratory tests, and clinic visits are of paramount importance (Kuntz et al. 2015). Patients and their support persons must be organized and disciplined to ensure that prescriptions are consistently filled and appointments attended. External aids to memory can be useful in managing these tasks and can range in sophistication from simple paper calendars or 7-day pill boxes to internet-mediated applications (Anglada-Martinez et al. 2015; Kuntz et al. 2015).

Psychological distress after transplantation is not uncommon and often linked to presurgical psychopathology and less nurturing environments (Dew et al. 2001). Disrupted feeding is associated with eating disorders in children who receive IT (Sudan 2010). Other conditions that appear linked to the development of psychological disorders include female gender, longer wait for transplant, and a maladaptive coping style (Dew et al. 2012). The three most commonly diagnosed post-surgical psychological disorders are depression, anxiety, and post-traumatic stress disorder. Depression rates after transplantation have been estimated to range from 5% to 25%, depending on the type of transplant and the time since surgery (Dew et al. 2001; Dobbels et al. 2008), and anxiety rates post-transplantation are estimated at 17–28% (Dew et al. 2001; Limbos et al. 2000). Importantly, post-transplantation depression has been associated with increased morbidity and mortality (Dew et al. 2001; Dew et al. 2015; Corbett et al. 2013). A recent review of 23 studies revealed that post-traumatic stress disorder after organ transplantation is fairly common (10–17%), and similar to depression, it is related to poor social support and pre-transplantation psychopathology (Davydow et al. 2015). Surprisingly, a single study conducted with veterans who received either a bone marrow transplant or solid organ transplant found no increase in mortality associated with serious mental illness such as schizophrenia, major depressive disorder, or bipolar disorder (Evans et al. 2015).

Psychological distress after transplantation, especially depression, anger, and hostility, is associated with decreased adherence (Cukor et al. 2008) and failures in self-care (Dew et al. 1999). The experience of medical complications, disruptions in relationships with caregivers, thoughts about the donor, and having expectations of the surgery disappointed also contribute to emotional upsets (Michaelsen and Arnold 2013). Immunosuppressant medications have been identified as contributing to psychological problems (Annema et al. 2015), and a new area of inquiry into the effect of

the gut biome on mood/mental function may have important implications for the psychology of IT.

Coping

Coping strategies are understood as ways by which people attempt to manage stressful or challenging situations and have been investigated in numerous populations, both ill and well. Coping is seen as varying on dimensions such as active vs passive, denying vs optimistic, and avoidant vs accepting. In transplant populations, the most adaptive coping appears to be action oriented, accepting, and optimistic, while the least adaptive included denial, disengagement, and giving up (Porter et al. 1994; Burker et al. 2005). After transplantation, avoidant coping (where the individual actively attempts to exclude troubling thoughts or memories from awareness) is associated with the development of psychopathology after surgery (Golfieri et al. 2007). Those authors conclude that for intestine transplant recipients, "optimistic coping strategies were most used, and most effective" and suggest that psychological support can be helpful in encouraging problem-focused approaches while discouraging maladaptive/emotional styles (Golfieri et al. 2007).

Quality of Life and Functioning

Quality of life and functioning are measured before and after transplantation to gauge psychosocial benefits of the procedure. For solid organ transplantation in general (kidney, heart, lung, liver), there are indications of a clear benefit from transplantation, peaking at the 6-month mark after surgery (Kugler et al. 2013). Although posttransplant health-related quality of life ratings certainly improve over those of pre-transplant, these gains do not restore recipients to ratings of well-being at the same level as the general population (Baranyi et al. 2013).

Medical complications are common in the IT population (Sudan 2014), and the procedure is associated with long recovery periods with recurrent hospitalizations (Rege and Sudan 2016). When they occur, medical complications are seen as driving lower quality of life scores, along with increases in psychological distress (Sudan 2010). Nevertheless, most studies on IT recipients show benefit as compared to patients who remain on parenteral nutrition (Pironi et al. 2012; Abu-Elmagd et al. 2012) with quality of life scores improving in parallel to gains in organ function (O'Keefe et al. 2007). Among the positive effects of IT are recipients' expansion of their view of themselves and the possibilities of their lives after transplantation (Golfieri et al. 2010). Other benefits include decreased anxiety, improved coping, better sleep, and more positive social relations (Abu-Elmagd et al. 2012). In a 2007 study, the authors exuberantly declared that quality of life after IT was "dramatically improved" over pre-transplant states (O'Keefe et al. 2007).

Despite these gains, challenges to IT recipients are apparent. Some experience decline in financial status, need for sleep aids, reduced physical functioning, and more depression (Abu-Elmagd et al. 2012). Challenges to social roles, particularly their redefinition as a consequence of transplantation, may impinge on the quality of social relationships (Golfieri et al. 2010). When present, depression was found to be the greatest predictor of diminutions of overall well-being in general transplant populations (Kugler et al. 2013).

Children who receive IT see themselves as similar to children in the general population across psychological, physical, and social domains (Rege and Sudan 2016). But their parents observe worse health and physical function (Sudan 2004; Andres et al. 2014; Fredericks et al. 2014; Mutanen et al. 2015). This difference may be explained by young children having less awareness of their status than do their parents, an explanation that is supported by more convergent ratings as the children age (Andres et al. 2014). When everyday life skills are assessed, pediatric IT recipients are shown to lag behind peers in the general population and, to a lesser extent, behind liver transplant recipients (Shellmer et al. 2013). Shellmer et al. found that observed decrements in adaptive functioning were associated with male gender and lower educational level of caregivers. Patients' health-related quality of life scores were

also seen to decline in the presence of abdominal pain, and the presence of both high frequency stooling and abdominal pain were associated with higher levels of parental stress (Mutanen et al. 2015), again underlining the contribution of physical function to assessments of quality of life.

Efforts at maximizing quality of life are focused on behavioral and medical interventions. Some investigators recognize immunosuppressant medication (especially tacrolimus) side effects for adverse neurocognitive and physical effects (Abu-Elmagd et al. 2012). Quality of life measures show enhanced well-being after mindfulness training for both recipients and their caregivers (Stonnington et al. 2016). The literature on transplant in general and IT in particular is rich with recommendations that treatment teams remain vigilant for the emotional health of patients and their families and offer avenues of assistance wherever needed (Gentleman et al. 2008).

Future Directions

Although still in its early stages, investigations into the contribution of gut microbiota to cognitive and affective functioning are under way. One hypothesis is that psychological stress affects intestinal flora populations, thereby altering the presumed feedback loop between the brain and gut (Petra et al. 2015). Research has shown an association between the presence of particular bacteria and diagnosis of depression, but these data are correlational, not causal (Aizawa et al. 2016). In a recent review of extant evaluations, a clear connection between psychiatric diagnoses and alterations in gut microbiota composition/function was not proved (Kelly et al. 2016). Further investigations may shed light on this intriguing puzzle and guide advances in treatment for patients with major disruptions to their gut, such as IT.

Conclusion

Intestinal transplantation is a psychologically stressful procedure that addresses far more distressing physical dysfunction. Candid pre-transplant communication with the treatment team can help to assess, educate, and prepare patients and their families for the events and requirements of surgery. Along with other specialists on the team, psychologists/mental health professionals contribute unique expertise, offering pragmatic avenues of amelioration for conditions that may hinder success.

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Pharmacologic Considerations in Multivisceral Transplantation

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Contents

Abstract

The complexity of multivisceral transplantation (MVT) extends beyond the operation itself. The introduction of superior immunosuppression, effective broad-spectrum anti-infectives, and a better understanding of how to treat complications have allowed the procedure to advance to the level of success seen today. Induction therapy with lymphocyte-depleting agents or IL-2 antagonists can prevent rejection within the acute posttransplant period and delay the exposure to toxicities associated with maintenance immunosuppression. With the introduction of tacrolimus,

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successful MVT became a reality. With tacrolimus and prednisone as the backbone, numerous immunosuppressive strategies continue to be explored as the search for a maximally effective, minimally toxic regimen continues.

Infection is the leading cause of morbidity and mortality in multivisceral transplant recipients. Broad-spectrum antibiotics against both gram-positive and gram-negative organisms are chosen to cover skin flora in addition to the enteric contents of the small bowel. Antifungal prophylaxis is frequently used, and prevention against cytomegalovirus must be implemented in those at the greatest risk. Even with the avoidance of both infection and rejection, recipients suffer from many debilitating symptoms frequently leading to readmission and significantly affecting quality of life. Managing each complication requires careful selection of pharmacologic agents to optimize patient outcomes and well-being.

Keywords

Immunosuppression · Cytomegalovirus · Multivisceral · Transplant · Calcineurin inhibitor · Induction · Infection · Prophylaxis · Maintenance · Complications

Introduction

The complexity of multivisceral transplantation (MVT) extends far beyond the operation itself. Pharmacologic management of these patients before, during, and after their transplantation is extremely complicated. The first multivisceral transplant procedure was performed in 1967, before the introduction of parenteral nutrition and when azathioprine and steroids were the only immunosuppressive medications available, rendering any chance of extended survival impossible (Lillehei et al. 1967). Since the first successful MVT performed in 1987 by Starzl's team at UPMC (Starzl et al. 1989), the introduction of superior immunosuppression, effective broad-spectrum anti-infectives, and a better understanding of how to treat complications have allowed the procedure to advance to the success we see today. It is clear, however, that much still remains unknown regarding the optimal approach to continue to extend graft and patient survival beyond what is today and improve the long-term quality of life of the recipients undergoing this complicated procedure.

Immunosuppression Strategies

The biggest barrier to successfully performing multivisceral transplant after the development of the technical procedure itself was the inadequacy of the immunosuppressive methods available at the time. With the introduction of cyclosporine, 30 years after the MVT technique was proven to be feasible, modest progress in survival was observed (Hoffman et al. 1990). It was ultimately in 1990, with the introduction of tacrolimus, when successful isolated intestine transplantation and MVT became reality. With tacrolimus and prednisone as the backbone, numerous immunosuppressive strategies have been and continue to be explored as the search for a maximally effective, yet minimally toxic, regimen continues.

In continued effort to eliminate rejection in the setting of a highly immunogenic graft, modifications to the tacrolimus-prednisone backbone by the addition of a third and even fourth immunosuppressive agent, has been trialed at many centers. It has been suggested, however, that the conventional addition of multiple maintenance immunosuppressive agents could actually defeat the body's natural tolerogenic mechanisms of graft acceptance, causing the recipient to be dependent on heavy-maintenance immunosuppression to prevent rejection long term (Reyes et al. 2005). This would lead to more complications from over-immunosuppression and more toxicities from the immunosuppressant drugs themselves. The attempt to prevent this paved the way to what we now refer to as induction immunosuppression being used in most centers performing MVT. In the modern era of solid organ transplant, the use of immunosuppression can be thought of in three distinct phases: induction, maintenance, and treatment of rejection.

Induction Immunosuppression

The use of induction therapy refers to the administration of very potent immunosuppressive agents, usually lymphocyte depleting in nature, during the initial posttransplant period, when the risk of hyperacute and acute rejection is the highest. Utilization of this approach spans all types of solid organ transplant to varying degrees and remains the current practice at the majority of centers performing multivisceral or intestine transplant today due to the high risk of rejection.

The goals of using induction therapy vary based on the type of organ being transplanted and the induction agents being used. In general, the modern approach of using induction therapy is to prevent rejection within the acute posttransplant period and delay the exposure to toxicities associated with maintenance immunosuppression. Centers previously relying on heavy-handed tacrolimus dosing in combination with long-term steroids prior to the use of induction have now been able to successfully reduce tacrolimus exposure and its unwanted toxicities, mainly nephrotoxicity, and eliminate the need for chronic steroids and their numerous associated complications.

The utilization of various induction agents has evolved as newer drugs have become available, and more evidence has surfaced showing decreased rates of rejection with tolerable effects on complications such as infection, posttransplant lymphoproliferative disease (PTLD), and graft versus host disease (GVHD) with specific agents. The most commonly used induction agents and their mechanisms of action can be seen in Table 1. In 2003, a report from the Intestinal Transplant Registry analyzed data from 61 programs on 989 grafts in 923 recipients to determine factors impacting graft and patient survival. When comparing the effects of no induction with the use of either anti-IL-2 antibodies (daclizumab or basiliximab) or T/B lymphocyte-depleting antibodies (rATG, alemtuzumab, or OKT3), induction therapy was found to be associated with both improved graft and patient survival, reaching statistical significance (Grant et al. 2005). The most recent report from the Intestine Transplant Registry, in which data was included from 2887 transplants performed on or before February 2, 2013, indicated that 72% of patients were induced with an IL-2 antagonist, an antilymphocyte product, or alemtuzumab. This rate has increased significantly over the years (Grant et al. 2015).

To date, there has been no head-to-head comparison of induction agents, so there is no consensus as to which regimen is superior. The studies that have been done comparing induction agents include small numbers of patients, are not standardized, and often compare various eras, thus are impacted by numerous other factors that change over an extended period of time. While the potent lymphocyte-depleting agents have shown a reduction in rejection, there has been continued concern as to the potential increase in infection and/or rates of posttransplant lymphoproliferative disease (PTLD) when compared to the non-depleting anti-IL-2 antibodies such as daclizumab and basiliximab, so studies are ongoing as to the best induction strategy. The possibility also exists that there may not be a one-fits-all or best strategy, and the ideal approach may differ based on donor and recipient characteristics such as indication for transplantation, risk of infection, and/or preexisting antibodies.

Maintenance Immunosuppression

Historically, maintenance immunosuppression in patients receiving a multivisceral transplant has consisted of multiple agents including a calcineurin inhibitor (cyclosporine or tacrolimus), steroids, and the addition of a third class with either an mTOR inhibitor (sirolimus or everolimus) or, less commonly, an antimetabolite (azathioprine or mycophenolate). The introduction of new, more effective immunosuppressant agents in addition to the widespread use of induction therapy as previously described has enabled a shift toward minimized maintenance immunosuppression. The results of this approach have shown significant improvement in posttransplant complications from over-immunosuppression and toxicity from the drugs themselves without an increase of graft rejection.

Table 1 Induction agents used in multivisceral transplant

Drug name		Classification	Mechanism of action
T/B cell-depleting agents			
Rabbit anti-thymocyte globulin (rATG)	Thymoglobulin®	Polyclonal T cell-depleting antibody	Targets numerous T cell markers inducing complement-mediated T cell clearance and modulation of T cell activation, homing, and cytotoxicity
Alemtuzumab	Campath®	Monoclonal T and B cell-depleting antibody	Binds to CD52+ on T and B lymphocytes, monocytes, macrophages, NK cells, and some granulocytes leading to antibody-mediated lysis
Muromonab-CD3	Orthoclone® OKT3	Withdrawn from the market due to decreased utilization	
Anti-IL-2 antibodies (non-depleting agents)			
Basiliximab	Simulect®	Chimeric monoclonal antibody	Targets CD25 blocking the alpha chain of the interleukin-2 (IL-2) receptor complex expressed on activated T lymphocytes
Daclizumab	Zenapax®	Withdrawn from the market due to decreased utilization	

Calcineurin Inhibitors

Similar to other types of organ transplant, calcineurin inhibitors (CNIs) remain the backbone of maintenance immunosuppression regimens, but tacrolimus specifically has shown superiority over its CNI counterpart cyclosporine. Tacrolimus is typically started immediately after transplantation and continued indefinitely barring any intolerable adverse effects. Goal therapeutic levels are the highest in the initial few months posttransplant, when the risk of rejection is most significant, then reduced after the first 3–6 months, and then further reduced from months 6 to 12 as tolerated. Levels are monitored frequently, especially in the initial postoperative period. Often, administration via the sublingual route is required at least initially, as patients are typically not taking anything by mouth for a number of days postoperatively. Calcineurin inhibitors have extremely variable absorption, making the sublingual route desirable, in efforts to achieve and maintain stable goal levels when the risk of rejection is the highest. It is important to note that doses must be reduced by one-third to one-half when converting from the oral to sublingual route of administration.

Toxicities associated with CNIs, especially at high doses, cause significant challenges. As patient survival after multivisceral transplantation has improved significantly, the occurrence of long-term toxicities has been more pronounced. Nephrotoxicity has been the most limiting toxicity associated with the use of calcineurin inhibitors leading to a focus on minimizing and even eliminating their use in other solid organ transplant populations. Neurotoxicity is also frequently seen, more commonly with tacrolimus, which can range in severity from fine tremors and headaches to seizures and coma. These effects are typically dose related and reversible upon dose reduction, but may warrant changing to an alternative agent in some situations. Other acute and chronic toxicities commonly seen with CNIs are listed in Table 2. Unfortunately, a maintenance immunosuppression agent with similar efficacy to the CNIs, but lacking the toxicities, is yet to be discovered.

Concomitant Maintenance Immunosuppressants

As previously described, the discovery of CNIs, specifically tacrolimus, has made long-term survival after multivisceral transplantation a reality. Unfortunately, due to high rates of rejection and associated graft loss, outcomes are still worse than those of other organ transplants such as kidney and liver. For this reason, as well as the toxicities seen with CNI therapy described previously, the addition of other immunosuppressants continues to be explored.

The most promising results published to date are with the addition of the mTOR inhibitor, sirolimus. The addition of sirolimus to tacrolimus either 1 month posttransplant or introduced in

Table 2 Adverse effects of maintenance immunosuppressant drugs used in solid organ transplant

	Nephrotoxicity	Bone marrow suppression	Neurotoxicity	Gastrointestinal	Hyperlipidemia	Hypertension	Posttransplant diabetes	Osteoporosis	Others
Cyclosporine (Gengraf®, Neoral®)	+++		++		+	++	+	+	Gingival hyperplasia
									Hirsutism
									Hyperkalemia
									Hypomagnesemia
Tacrolimus (Prograf®)	+++		+++		+	+	++	+	Alopecia
									Hyperkalemia
									Hypomagnesemia
Azathioprine (Imuran®)		+++		++					Liver toxicity
									Pancreatitis
Mycophenolate mofetil (Cellcept®)		++		+++					Congenital defects
Sirolimus (Rapamune®)/ everolimus (Zortress®)		++			+++				Impaired wound healing
									Oral ulcers
									Pneumonitis
									Proteinuria
Corticosteroids					++	++	++	+++	Gastric ulcers
									Osteoporosis
									Psychosis
									Suppression of HPA axis

patients with CNI-associated complications has resulted in fewer or less severe episodes of acute cellular rejection in three small single-center studies (Florman et al. 2002; Gabardi et al. 2011; Lauro et al. 2007). The effects of mTOR inhibitors on wound healing limit its use immediately after transplantation. Other limiting toxicities are listed in Table 2.

Antimetabolites have shown promising results as adjunct agents in liver and kidney transplant populations, primarily after the introduction of mycophenolate as an alternative to azathioprine. Mycophenolate has a favorable toxicity profile in that it has not been shown to cause the nephrotoxicity seen with the CNIs and has less myelosuppression than the other antimetabolite, azathioprine. Unfortunately, the primary toxicity seen with mycophenolate is gastrointestinal toxicity, making its use in intestine and multivisceral transplantation complicated and controversial, as it makes differentiation between drug toxicity and dysfunction of the intestine graft very difficult.

Steroids remain a component of maintenance immunosuppression after multivisceral transplantation, but there has been a trend toward weaning to very low doses and eventually discontinuing them altogether after the first 6 to 12 months in patients without signs of rejection. Steroid avoidance is increasingly important as the length of survival increases due to the large number of toxicities associated with chronic use, particularly in the pediatric population. Novel implementation of IL-2 inhibitors as a component of maintenance immunosuppression has been explored by one center with favorable results. An anti-IL2 receptor antibody was given to intestine and MVT recipients not receiving a liver graft. In the liver-excluding transplants, there was a significant decrease in acute rejection and a higher rate of graft survival at 3 years despite more of these patients having a positive crossmatch (Kubal et al. 2013).

Anti-infective Strategies

Infection continues to be the leading cause of morbidity and mortality in multivisceral transplant recipients and remains the one factor that has not improved over time (Grant et al. 2015). Infections occur almost universally, with bacterial infections occurring in >90% of recipients (Silva et al. 2015; Loinaz et al. 2003) and often with multidrug-resistant pathogens (Primeggia et al. 2013). Viral and fungal infections have decreased in incidence over time with the widespread use of prophylactic antiviral and antifungal agents, but still commonly occur, and their occurrence is associated with significant impacts on morbidity and mortality. Some of the factors putting this population at a higher risk for infection are the use of potent, high-dose immunosuppression necessary to prevent and/or treat rejection, the use of long-term central catheters and parenteral nutrition, numerous extensive surgical interventions, and recurrent and/or prolonged hospitalizations due to complications. Also unique to transplantation of the intestine, unlike other transplanted organs that are sterile, the intestine is contaminated with numerous microbes that make up the normal gut flora. Any impairment of mucosal integrity that occurs in the presence of rejection can easily cause translocation of these microbes leading to serious infection.

Infection in solid organ transplant is typically categorized by the time frame in which certain types of infection are more likely to occur, early (0–1 month), intermediate (1–6 months), and late (>6 months), although the numerous unique characteristics of multivisceral transplant recipients make these time frames less clear than in other types of organ transplant (Green 2013). Nonetheless, centers use these basic ranges to help guide the choice of antimicrobial prophylaxis, but the duration of prophylaxis is often extended compared with other types of organ transplant.

Perioperative Antibiotics

Antibiotic utilization measures put forth by the Surgical Care Improvement Project (SCIP) do not include transplant centers. In fact, there is no governmental or medical guidance as to what constitutes appropriate antimicrobial prophylaxis in transplant patients at all. In the multivisceral

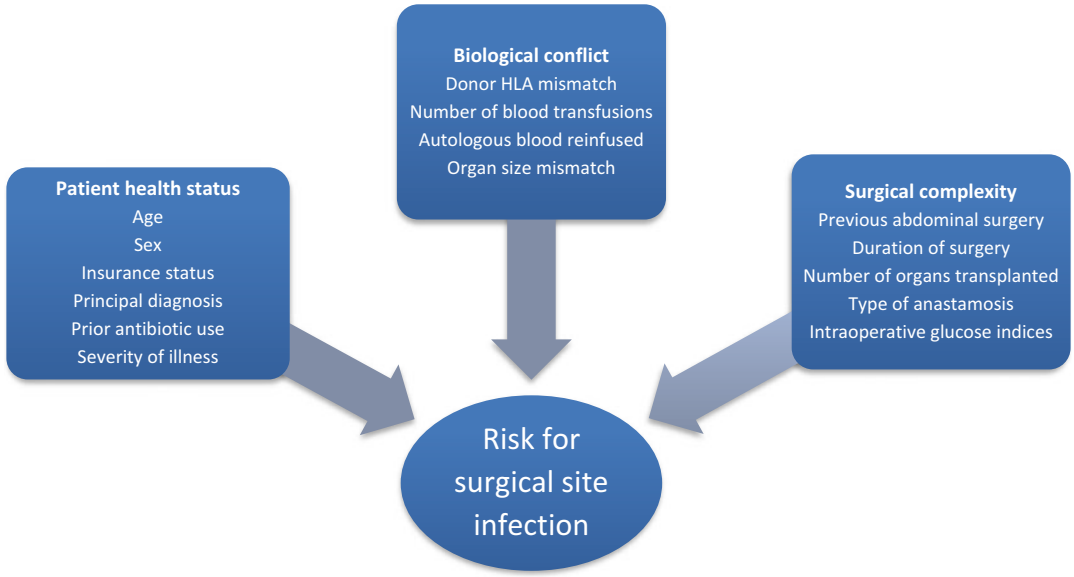

Fig. 1 Conceptual model for risk for surgical site infection (Kettelhut and Van Schooneveld 2010)

transplant population, no studies have been done that are specifically designed to help guide perioperative antibiotic selection or duration. A number of transplant-related risk factors specific to the liver and multivisceral transplant population were described in an article out of the University of Nebraska Medical Center in 2010. The risk factors were categorized into three groups: (1) patients' health status, (2) biological conflict, and (3) medical factors. Specific criteria under each of these groups are shown in Fig. 1 (Kettelhut and Van Schooneveld 2010). The complexity of both the multivisceral transplant population and the surgical procedure itself would likely characterize these patients as high risk universally. Broad-spectrum antibiotics covering both gram-positive and gram-negative organisms are chosen based on their activity against skin flora in addition to the enteric contents of the small bowel. This typically includes the use of vancomycin to cover methicillin-resistant *Staphylococcus aureus* and susceptible *Enterococcus* species, in addition to an agent with activity against resistant gram-negative organisms as well as anaerobic bacteria such as piperacillin-tazobactam or meropenem. It is worth noting that selection of antibiotic prophylaxis should be individualized in those patients with documented infections prior to transplant. A patient's infection history should be obtained when possible and susceptibilities reviewed to assure coverage would be adequate to prevent reinfection from organisms that may already be present.

In the absence of guidelines, the duration of perioperative antibiotic prophylaxis remains center specific but often ranges from 3 to 7 days postoperatively (Timpone et al. 2013). Some reports suggest continuing broad-spectrum antibiotics until the integrity of the transplanted graft can be confirmed by surveillance enteroscopy, although the benefit of this has not been confirmed. The risk of inducing resistance must be considered in a population with a high rate of resistant pathogens at baseline. The infectious disease guidelines put forth by the American Society of Transplantation emphasize the importance of eliminating unnecessary antibiotic exposure in the effort to prevent the emergence of multidrug-resistant organisms. These guidelines recommend that peritransplant antibiotic prophylaxis should not be used beyond 48 h posttransplant with the exception of lung transplant recipients only (van Duin et al. 2013).

Prevention of Fungal Infections

The incidence of invasive fungal infections (IFI) has been reported to be higher in recipients of a small bowel transplant compared to any other type of solid organ transplant (40–59% incidence) (Singh 2000). More recent studies have demonstrated a much lower rate, likely reflecting the use of antifungal prophylaxis as well less potent immunosuppression. Risk factors for IFI specific to this population include the presence of long-term central venous catheters, use of parenteral nutrition, exposure to broad-spectrum antibiotics, immunosuppression used for induction and treatment of rejection, anastomotic leaks and fluid collections, and the need for multiple surgical procedures. *Candida* species is responsible for the majority of IFI (80–100%), with *Candida albicans* predominating (Florescu et al. 2010) (Silva et al. 2015). Invasive fungal infections can occur at any time after MVT. Intra-abdominal infections with invasive candidiasis are usually seen within the first month posttransplant (median of 9 days), whereas the median occurrence of candidemia has been reported as 163 days posttransplant (Florescu et al. 2010). Oral candidiasis also frequently occurs, often with accompanying esophagitis, likely impacted by the use of steroids. The choice and duration of antifungal prophylaxis continue to vary between transplant centers. The American Society of Transplantation (AST) guidelines recommend the administration of fluconazole 400 mg/day or liposomal amphotericin when there is suspicion of non-albicans *Candida* species for a minimum of 4 weeks or until the anastomosis has completely healed provided there is no evidence of rejection (Silveira et al. 2013). Particular attention must be given when the use of azole antifungal agents is initiated and discontinued due to the significant interaction with calcineurin inhibitors and numerous other medications. Prevention of oral candidiasis can also be attained with the use of fluconazole, although often the administration of nystatin oral suspension can also provide adequate prevention.

Antiviral Prophylaxis

Multivisceral transplant recipients are at risk for a number of viral infections, often leading to viral enteritis affecting the transplanted graft. Cytomegalovirus (CMV) is the most common infectious complication in all types of solid organ transplant, so specific recommendations for prophylaxis have been established. Because intestine and multivisceral transplant patients are among the highest at risk for cytomegalovirus, prophylactic strategies are imperative. Unfortunately, this population was not included in any of the clinical trials assessing preventive strategies, so current practice has been based on the information from published single-center experiences.

Two approaches to CMV prevention currently exist: a preemptive approach involving routine monitoring of CMV qualitative polymerase chain reaction and initiating treatment upon detection of the virus and a universal approach which involves administration of antiviral agents to all patients to prevent infection. Most centers use a hybrid of these two approaches meaning that universal prophylaxis is given to those deemed to be at the highest risk for a certain length of time, and the preemptive approach is used in those at a lower risk or after prophylactic antiviral medications have been discontinued (Florescu et al. 2014).

Current guidelines recommend universal administration of either intravenous ganciclovir or oral valganciclovir in multivisceral transplant recipients at high or moderate risk based on CMV serostatus for anywhere between 3 and 12 months after transplant (Kotton et al. 2013; Razonable et al. 2013). The use of intravenous ganciclovir is recommended specifically for the first 14 days posttransplant until the patient is tolerating enteral intake and the integrity of the transplanted intestine has been confirmed. Oral valganciclovir is often preferred for continuation of prophylactic therapy due to the once-daily dosing and ease of

administration. Many centers also use CMV immune globulin (Cytogam®) in addition to antiviral prophylaxis, but a standard regimen or duration of use has not been established and varies significantly between centers. A recent single-center study has suggested that the use of Cytogam in the population at highest risk for CMV infection may have a protective effect, although this remains controversial, and cost is a significant barrier to routine use of this agent (Nagai et al. 2016).

In addition to the prevention of cytomegalovirus infection, routine prophylaxis with ganciclovir or valganciclovir also offers some protection against other types of viral infections such as HSV, VZV, EBV, and HHV. In centers that do not routinely give CMV prophylaxis to patients at low risk of CMV infection, the administration of oral acyclovir or oral valacyclovir is sometimes used to prevent the aforementioned non-CMV viral infections in patients deemed to be at risk. An in-depth discussion of cytomegalovirus and other viral infections has been described in the chapter entitled ▶ "Viral Infections After Intestinal Transplantation."

Supportive Care

Optimal care of the multivisceral transplant recipient requires a multidisciplinary approach to management, ideally with the participation of the surgeon, gastroenterologist, intensivist, pharmacist, and dietician in addition to dedicated nursing care, preferably by nurses with experience in caring for these patients. Recipients of multivisceral transplants tend to have more complicated posttransplant courses when compared to recipients of an isolated organ as they suffered from multiple organ failure, often for extended periods of time, before being transplanted (Hauser et al. 2008). Achieving and maintaining hemodynamic stability, providing appropriate pain management, continuously monitoring graft function, and encouraging early mobilization take priority within the first 72 h or so after transplantation. As survival rates continue to improve, a shift toward prevention and management of long-term complications will be pursued in order to allow patients to live as normal a life as possible. A detailed discussion of this can be found in the chapter entitled "MVT: Complications."

Hemodynamic Support

Achieving hemodynamic stability can be very challenging in this population, not only in the immediate postoperative period but also on a long-term basis. Large fluid shifts are not uncommon postoperatively due to blood loss, dehydration, vascular clamping, long ischemic time, intraoperative visceral exposure, intestinal denervation, ischemic damage, and lymphatic disruption (Siniscalchi et al. 2008). Despite attempting to optimize nutrition prior to transplant, patients are often malnourished with minimal protein stores, leading to significant third spacing of fluids and intravascular dehydration despite fluid replacement. The administration of boluses of crystalloid and often colloid such as albumin is crucial to maintain adequate blood pressure and organ perfusion. Despite fluid resuscitation, vasopressors such as norepinephrine and vasopressin are often needed in addition. Patients continue to receive volume, while nutrition is initiated in the form of parenteral nutrition in the early postoperative period. This is done because initiation of enteral nutrition must be pursued cautiously after graft integrity has been confirmed, and achieving nutrition goals enterally can take days to weeks after transplant.

Dehydration remains a significant risk in the multivisceral transplant recipient even months to years after transplantation and is one of the leading causes of readmission. After stabilization of the patient, determining the cause of dehydration is crucial in preventing additional complications, although this can be challenging as there are many posttransplant complications affecting the gastrointestinal tract resulting in dehydration, which will be discussed next. If renal dysfunction is present in the setting of dehydration, monitoring for reversal with the administration of fluids is necessary to rule out any additional causes of renal dysfunction such as that seen with calcineurin inhibitors, discussed previously.

Gastrointestinal Dysfunction

Nausea, vomiting, diarrhea, constipation, and pain are the most common complaints of multivisceral transplant recipients. Management of nausea and vomiting can usually be achieved but often requires frequent administration of drugs from multiple pharmacologic categories. Scheduling selective 5-HT3-receptor antagonists such as ondansetron can help prevent nausea and vomiting, but administering this class of medications after the patient is already experiencing symptoms will likely be inadequate. Adjunct agents such as promethazine, prochlorperazine, and metoclopramide are typically needed to resolve symptoms.

Prevention and treatment of diarrhea in this population can be extremely complicated, and determining the cause of diarrhea is crucial to dictate the appropriate path to management. Common causes of diarrhea include, but are not limited to, enteral tube feeding formulas, bacterial or viral infections, bacterial overgrowth, and rejection of the transplanted graft. Patients with temporary or permanent ostomies tend to have more severe symptoms from excessive ostomy output, often leading to dehydration and electrolyte imbalances and sometimes leading to the requirement of maintenance intravenous fluids outside of hospital. Antidiarrheal medications can be initiated only after infectious causes have been ruled out. Both loperamide (Imodium®) and diphenoxylate-atropine (Lomotil®) can be used in combination, alternating throughout the day, and when symptoms are exacerbated. The addition of tincture of opium can also be helpful in controlling diarrhea and is usually well tolerated. Ultimately, each transplant recipient must be evaluated carefully, and the choice and dosing of medications must be individualized to their specific symptoms.

Constipation occurs less often than diarrhea but can also lead to numerous complications and significantly impact quality of life. Frequent administration of opioid narcotics is one of the most frequent precipitating factors but can be one of the most complicated factors to manage. Excess antidiarrheal medications can also lead to constipation, so a balance of these two symptoms must be achieved to assure the best quality of life. Severe or recurrent constipation may warrant additional motility studies after medication-related causes have been excluded. Pro-motility agents such as metoclopramide can be helpful in patients with delayed gastric emptying.

Pain Management

Adequately controlling pain after multivisceral transplantation is often extremely frustrating for both the provider and patient. Many patients pursuing this type of transplantation have undergone numerous surgical procedures, have been frequently hospitalized, and have a very poor quality of life with varying degrees of chronic pain. Therefore, many patients have received high doses of opioid pain medications for months to years before being considered for transplant. Unfortunately, chronic pain medication use, particularly with opioid medications, will significantly impact posttransplant morbidity, so it is a matter requiring serious consideration and attention. Although the patient may have developed a tolerance to the unwanted adverse effects of opioid pain medications, the tolerance is not transferred to the transplanted bowel. Exposing an opioid naïve transplanted graft to high levels of narcotics can significantly contribute to delayed graft function through the direct effects of opioids on decreasing bowel motility. In this situation, minimizing pain medications leaves the patient's pain uncontrolled, which can lead to a seemingly impossible situation for the provider.

The most effective way to prevent this difficult situation is to be aggressive prior to the time of transplant. An effective approach adopted by some transplant centers is to have the patient sign an opioid contract agreeing to wean off opioids or at least not exceed a predefined dose limit for a specified time prior to being listed and then after being officially put on the list for transplant. Weaning off these agents is not easy but can be done by those who are determined, especially if it will be potentially lifesaving.

Conclusion

The advances in pharmacologic treatment have enabled long-term survival after multivisceral transplantation to become a reality. Recent immunosuppressive strategies have shown modest improvement in preventing rejection while lessening the long-term toxicities associated with heavy-handed maintenance immunosuppression. Targeted anti-infective agents are widely utilized to prevent perioperative infections and to prevent opportunistic bacterial, viral, and fungal infections in patients identified to be at the highest risk throughout the time period when these complications are more likely to occur. Despite all of the advances made throughout the years, there still has yet to be any sort of conclusion as to the optimal way to manage these patients post-transplant. The risk of complications due to infection and rejection remains very high. Even when those complications are avoided, patients are frequently troubled by symptoms of nausea, vomiting, diarrhea, dehydration, and toxicities secondary to immunosuppression making it difficult for them to live a normal life. With more knowledge about this complex procedure and associated disease states, hopefully the outcomes of multivisceral transplant will one day reach those of liver and kidney transplantation. Certainly, great strides have already been made since the first procedure was performed.

Cross-References

- ▶ Modern Parenteral Nutrition
- ▶ Viral Infections After Intestinal Transplantation

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Nutrition Considerations in Multivisceral Transplantation

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Abstract

Nutritional management of patients who have undergone multivisceral transplantation is complex and includes maximizing nutritional status prior to transplant, weaning parenteral nutrition (PN) while simultaneously advancing enteral nutrition (EN), managing fluid status, reintroducing and/or advancing oral diet, continuously monitoring nutritional status, conducting patient education, and finally achievement of nutritional autonomy, free of PN and EN. Nutritional autonomy, the ultimate goal in intestinal transplantation, requires a multidisciplinary team including a qualified registered dietitian. This chapter will discuss the specific role of the dietitian in the nutritional management of these patients.

Keywords

Nutrition · Dietitian · Parenteral · Enteral · Transplant · Multivisceral · Growth · Diet · Autonomy · Multidisciplinary

Introduction

Nutrition management is one of the key components of multivisceral (MVT) transplant management. The majority of patients in need of this type of transplant have intestinal failure with irreversible consequences related to parenteral nutrition. The transplanted intestine has the unique ability to restore digestive and absorptive function of the gastrointestinal tract (Chapman et al. 2016). Successful intestinal transplant should not only be defined by patient and graft survival but achievement of nutrition autonomy. Over the past two decades with developments in immunosuppression and surgical techniques, MVT has evolved and become a recognized and viable treatment option for patients with intestinal failure. International data reveals that 67% of patients cease PN by 6 months after transplant (Grant et al. 2015). Centers have reported that 90% of patients who survived the first 6 months achieve nutritionally autonomy (Sudan 2004). However, little is known about the best practice options in order to achieve this with a population that often experiences a wide array of complications. The optimal nutritional treatment after transplant is currently based on expert opinion and individual center experience. Dietetic practitioners agree that more research and evidence-based protocols are needed in this evolving field.

Pretransplant

Intestinal failure occurs when an individual is unable to meet their nutrition and hydration needs, and supplementary parenteral nutrition and/or intravenous fluid support is required. The care of these patients is extremely time consuming and challenging which requires an experienced multidisciplinary team. Some patients with intestinal failure are managed on PN for many years without complications and have a reported good quality of life. Others develop life-threatening complications such as stage intestinal failure-associated liver disease (IFALD), loss of venous access, and/or frequent line-related sepsis.

The primary diagnosis for intestinal transplant in adults and children is short-bowel syndrome. Underlying causes for this include Crohn's disease, trauma, ischemia in adults and gastroschisis, volvulus, and necrotizing enterocolitis in children. Furthermore, radiation enteritis along with intestinal dysmotility is additional reasons for intestinal failure (Grant et al. 2015). Candidates for transplant include patients who need liver transplant with portal vein thrombosis and patients with neuroendocrine tumors.

There are three main types of grafts transplanted: isolated intestinal transplant, modified multivisceral (MMVT – stomach, pancreas, small bowel), and multivisceral (MVT – liver, stomach, pancreas, small bowel). A partial segment of the colon can also be included.

Isolated intestinal transplant is indicated for patients who have irreversible gut failure with no other irreversible organ damage. A combined liver-intestine transplant is indicated for patients who have a combination of intestinal failure, PN-associated liver failure, and liver failure with portal and mesenteric venous thrombosis

(Kocoshis et al. 2004). Either full or modified multivisceral transplant is indicated for patients with disorders such as dysmotility syndromes, unresectable abdominal tumors, hereditary neoplasms, or diffused vascular thrombosis (Matarese 2010).

An isolated intestinal transplant is the preferred surgical option because there is no shortage of decreased donor organs and, if needed, the graft can be removed without compromising the function of other abdominal organs (Avitzur and Grant 2010). There has been a significant trend toward isolated intestinal transplant over the past 7 years due to the development of specialized intestinal rehabilitation centers (Grant et al. 2015). The treatment options and clinical expertise in the management of intestinal failure have improved reducing the risk for intestinal failure-related liver disease (IFALD) and decreasing the need for transplantation of additional organs. These options include surgical techniques, growth hormone therapy, and omega-3-based lipid emulsions.

Evaluation

Once the decision to proceed with transplantation is made, the goal during the preoperative stage is to optimize nutritional status. A registered dietitian conducts a thorough assessment of the candidate's nutrition status including a diet history, physical assessment, and objective parameters as part of the transplant evaluation process.

Nutrition History

A diet history is obtained to evaluate the patient's usual intake or feeding and swallowing development in the case of pediatrics. Detailed notes are taken to analyze the quantity and types of foods consumed, in addition to diet modifications, and presence of anorexia or dysphagia. Gastrointestinal symptoms are also noted, such as abdominal pain, nausea, vomiting, bloating, constipation, diarrhea, steatorrhea, and ostomy output (Weseman 2002). It is also essential to record any nutrition support (whether enteral or parenteral) utilized currently or in the past. Questions need to be asked about the duration of therapy and if fluids or electrolytes were added to the mixtures to supplement the feedings. The goal of the nutrition assessment is to identify any macronutrient and/or micronutrient deficiencies and determine goals and a plan to optimize nutrition status prior to the intestinal or multivisceral transplant (Nompleggi and Bonkovsky 1994).

Physical Assessment

Candidates for intestinal transplant should be evaluated and monitored based on physical signs of malnutrition and efficacy of home nutrition support. Current weight, usual weight, weight changes, body mass index (BMI), and percent ideal body weight (IBW) should all be discussed with the patient. For the pediatric population, growth measures should be plotted and followed over time. These include weight for age, length for age, and weight for length for patients <2 years old and weight, height, and BMI for those >3 years old. Measurement of midarm circumference and triceps skinfold thickness may also be utilized (Nucci et al. 2010). Furthermore, subjective assessment of muscle wasting (temporal or skeletal) and loss of subcutaneous fat and muscle help to determine the type and degree of malnutrition. Physical signs of micronutrient deficiencies such as severely dry skin, cheilosis, glossitis, tetany, and hair loss should also be recorded. Lastly, an assessment of edema, ascites, and loss of nutrients due to high ostomy output, high output fistulas, or diarrhea should be noted given that they can significantly affect nutritional status.

Objective Parameters

A thorough evaluation of objective parameters must be completed to develop a nutritional plan. Serum nutritional laboratory values commonly found to be deficient in this population must be obtained. Objective parameters include a

complete assessment of fat-soluble and water-soluble vitamins, trace elements, iron studies, as well as carnitine serum levels if possible.

Preoperative Nutrition Care

As documented in the liver transplant population, combined liver/small bowel transplantation in a patient with malnutrition leads to reduced graft function and increased incidence of bacterial infections (Weseman 2002). Efforts should be made to optimize nutritional status, preserve hepatic and renal function, and keep the patient free from infection until organs become available and the patient is transplanted (Fryer et al. 2003). Clinicians should know that most patients experience weight loss in the first year after transplant. In fact, a 25% body weight loss has been reported (Middleton et al. 2014).

Managing the macronutrient portion of a patient's PN prescription is challenging, especially in the presence of a damaged liver (Kocoshis et al. 2004). Oftentimes, patients require additional IV fluids along with their PN in order to prevent frequent dehydration and kidney damage. Trace elements and vitamin levels should be assessed and corrected prior to transplant. It is important to have candidates undergo bone density studies to assess baseline status prior to transplant.

Prior to surgery, transplant candidates are given an explanation of the postoperative nutrition support by the registered dietitian. The patient should be aware of a feeding tube placed postoperatively and the possibility of an ostomy.

In addition, the registered dietitian explains what symptoms the patient might experience after surgery, as the diet is advanced.

Posttransplant Care

The main goals of nutrition management in any transplanted patient in the acute posttransplanit phase are as follows: establish adequate nutrient intake to replete lost nutrition stores, provide substrate to support the body's ability to fight infection, heal surgical wounds and anastomoses, and supply energy to allow a patient to participate in physical therapy and activities of daily living (Matarese et al. 2007). Poor nutritional status complicates transplantation surgery by increasing morbidity and mortality. Malnutrition is prevalent in end-stage organ failure and good nutritional status continues to be a major issue in the post-transplant phase.

A goal specific to intestinal transplant is to restore full nutritional autonomy that requires completion of the adaptation process that occurs between the residual native gut and the engrafted viscera (Matarese et al. 2007). The surgical procedure affects enteric function by causing extrinsic denervation, disrupted neural activity, disrupted lymphatic drainage, and graft reperfusion injury (Silver and Castellanos 2000). A gradual progression of transitions from the parenteral to enteral route is used to achieve nutrition, along with fluid and electrolyte support. Nutrition protocols for the post intestinal transplant population vary among transplant centers. The majority of published papers provide nutrition information on what is typically done at centers with the most experience. Unfortunately, little is known about the adaptation process, and there is a gap in the literature on what specifically the universal protocol should be. Over the years centers have become more aggressive with immunosuppression regimens and surgical techniques, which have allowed for more liberal nutrition support and oral diets.

Parenteral Nutrition (PN)

PN continues to be the primary source of nutrition in the early postoperative period and is generally started within 24–48 h after the procedure. The prescription is likely to change from the order used during the pretransplant phase. The high volume of fluid needed for high losses will no longer be needed to help sustain the patient (Matarese 2010). Calorie and protein needs are likely to be higher in the postoperative phase to support hypermetabolism and hypercatabolism needed for healing and recovery. A patient's pre-surgical or estimated dry body weight is used to

calculate calorie and protein needs (Weseman 2002). Calories supplied are generally 30–35 kcal/kg/day and 1.5–2.0 g of protein/kg/day for anabolism. Nitrogen losses can be measured with nitrogen balanced studies to assure anabolism is being achieved. Requirements of the pediatric patient will vary based on the child's age, weight, and growth status. Caloric needs may range from 70% to 120% of estimated requirements, while protein needs are 150% of estimated needs (Nucci et al. 2010).

The first goal after the intestinal transplant is to wean the patient off of PN. In the majority of cases, weaning occurs within the first 3–4 weeks after transplant in the adult transplant population, unless there are complications that arise. Examples of reasons why PN would need to be prolonged are rejection, infections (i.e., cytomegalovirus), anastomotic leaks, and surgical setbacks (Weseman 2002). In addition, PN may need to be restarted during periods of moderate to severe rejection or enteric infections.

Enteral Nutrition (EN)

Timing of initiation of enteral feeding, the route of administration, along with the type of enteral feeding formula used vary according to individual transplant centers' protocols. Methods of feeding routes include a nasogastric tube, a naso-jejenal, a gastrostomy tube, or a jejunostomy tube. Delayed gastric emptying is commonly observed postoperatively and can be overcome with the use of jejunal feedings and prokinetic drugs. Most adult patients do well with a temporary NJ tube but surgically placed gastrostomy, jejunostomy, or GJ tubes should be considered in children or adults with significant eating problems that are identified in the pretransplant phase. However, most agree that EN should be initiated as soon as possible. There is little data to suggest that there are specific problems with enteral nutrition tolerance even soon after the transplant procedure (Horslen 2006). Early enteral feeding is necessary to promote gut trophicity as well as to maintain the mucosal barriers which will help optimize function of the gut and prevent bacterial translocation (Colomb and Goulet 2009). More recent studies suggest that enteral nutrition increases survival rate and decreases the risk of rejection (Wang et al. 2013; Colomb and Goulet 2009). Upon evidence of bowel function with either a bowel movement or ostomy output, enteral feedings should be started. This normally occurs within 3–7 days after the transplant.

Not unlike the timing of enteral nutrition, there are no clear guidelines on the type of formula to use. Clinical experience, patient tolerance, and quality of graft direct the enteral product selection. Some centers use elemental formulas that contain free amino acids, while others use a more aggressive approach and use intact formulas containing whole proteins. A formula that contains MCT is beneficial due to the impaired fat absorption during the early stage as well as high nitrogen content due to the patient's elevated protein needs for wound healing. The patient can be transitioned to a more intact formula prior to discharge. If the patient needs to be sent home on enteral nutrition, the formula choice upon discharge varies depending on each patient's specific needs. The enteral formula can be adjusted according to oral intake and fluid needs, along with restrictions of any kind. The fat can be further restricted in the presence of an identified chylous leak. In addition, the potassium can be limited when serum potassium levels are elevated as a result of the immunosuppressive drug tacrolimus. There is no documented experience with the safety of immune-modulating formulas at this time. Chylous ascites can be an early complication due to lymphatic ducts being severed. There has been a controversy as to whether a low-fat enteral formula is necessary as centers report a low incidence of chylous ascites with an intact formula containing mostly long-chain triglycerides.

The tube feeding is started at full strength at 5 mL per hour, and the rate should be increased slowly at 5–10 mL increments per day. If ostomy or stool output increases significantly, formula advancement can be held and antidiarrheal agents may be provided. As the EN rate is increased, the PN is tapered off. Clinical experience, patient tolerance, and quality of graft guide the selection

guide the advancement of tube feeding rate. Further clinical research is required to better identify the ideal enteral formula that maximizes the earlier use of intestinal allograft absorptive capacity. In general, those patients who receive isolated intestine transplant tolerate enteral feeding better than those who receive multiple visceral organs.

Fluids

The fluid status of the patient is one of the most important components of intestinal rehabilitation. Careful monitoring of the patient's weights, daily fluid intake, and output is essential. This includes keeping a close eye on adjustments of fluids from PN, EN, oral intake, and supplemental IV fluids. Output also needs to be monitored from the nasogastric or gastric tubes, urine, emesis, wound losses, ostomy, or bowel movements. The importance of educating recipients to monitor their ileostomy losses, fluid intake, and urine volumes cannot be overstressed as adequate hydration is essential in their long-term success (Weseman 2002). In some cases, patients will require intravenous fluids or administration of additional water or oral rehydration solutions flushed through the patient's feeding tube to hydrate them if they have trouble consuming adequate fluid volumes in the posttransplant phase. In cases of high stool losses, agents to aid in slowing transit time such as loperamide, lomotil, pectin, or other soluble fibers are administered (Reyes et al. 1993). Supplementation of magnesium, sodium, bicarbonate, and zinc are commonly needed due to increased losses in ostomy output and/or medication interactions (i.e., tacrolimus commonly causes hypomagnesemia). With recent inclusion of the donor colonic segments and the ileocecal valve with transplant, recipients are able to maintain hydration with more ease.

Oral Diet

The oral diet is typically started within the first 7–10 after surgery but has been reported to start as late as post-op day 14. In most cases this is done before tube feeding goal rates are achieved. Some adult patients are anxious to eat as they have struggled with oral intake for many years.

A clear liquid diet is initiated and patients are encouraged to consume small amounts of isotonic fluids such as tea, sugar-free beverages, and gelatin. The diet is quickly advanced to include complex carbohydrates, cooked and peeled fruits, low-fiber vegetables, and lean meats. Some centers recommend specific dietary restrictions such as refined sugars, lactose, and/or high fat foods due to intolerance as evidenced by increased ostomy output. Food allergies are not uncommon in the children posttransplant. Most recipients can liberalize their diet to a regular diet within 4–6 weeks posttransplant. Patients are advised to eat small, frequent meals. Careful monitoring of caloric and protein intake is required at this time. Continuous enteral nutrition is eventually transitioned to nocturnal feedings in order to maximize the patient's oral intake. Discontinuation of the enteral nutrition therapy is done when the patient is able to meet the majority of their calorie and protein needs with their oral intake. This timing varies considerably among individual patients but generally occurs within 3–8 weeks after transplantation for adults but they can continue for months to even years for children. See Table 1 for a summary of progression of nutrition care posttransplant.

After transplant some patients are eager to eat, while others may experience aversion to food because of months to years without eating. This is especially true in the pediatric population. It is common for patients to have many barriers to eating after years of negative consequences associated with oral intake such as pain, nausea, vomiting, bloating, constipation, and/or diarrhea. For recipients who are not accustomed to eating, the slow reintroduction of food will require additional support and encouragement.

The aid of prokinetic agents (i.e., Reglan) and appetite stimulants (i.e., Marinol) can aid in the transition to oral nutrition for patients with gastroparesis and anorexia (Rovera et al. 2003). Consultation from an occupational and/or speech therapist may be required for pediatric patients who have developed oral aversions.

Table 1 Progression of nutrition support in transplant patients

PN	Start within 24–48 h post-op
	30–35 kcals/kg of IBW of presurgical or est. dry wt
	50–70% total calories as carbohydrates
	<5 mg CHO kg/min
	Monitor fluid, electrolytes closely
	Begin weaning when 50% of calories are met enterally
	PN support is case specific but may be required for 3–6 weeks posttransplant
EN	Start 3–7 days post-op
	Initiate full strength at low rate
	Increase rate slowly by 5–10 mL increments per day
	EN is typically done into a jejunal tube
	Use isotonic, high nitrogen formula
	Wean PN support as EN is increased and tolerated
	EN feeding supplementation is required depending on oral intake and is case specific
	Continue IV fluid and oral rehydration supplementation as needed for hydration
Oral intake	Start clear liquids within 1–2 weeks of surgery
	Allow isotonic liquids in the first stage
	Advance as tolerated to a low-fiber, low-sugar, moderate-fat diet for 2–3 weeks
	Encourage small, frequent meals
	Prokinetic agents and appetite enhancers may be helpful
	Cycle EN to nocturnal when oral diet is tolerated and providing 25–50% of needs

Other Considerations of Nutrition Management

Side effects of immunosuppression therapy may include hyperglycemia, hyperkalemia, hypomagnesemia, hypertension, and hyperlipidemia that warrant changes in nutrition therapy of diet. Detailed information on immunosuppression medications and side effects can be found in the pharmacologic chapter of this book.

Food safety is an important component to consider as infection is the leading cause of morbidity and mortality in multivisceral transplant recipients (Grant et al. 2015). All members of the transplant team share responsibility to educate patients on long-term immunosuppression drugs and how to prevent infections. The registered dietitian is the expert in providing food safety guidelines to transplant recipients, their caregivers, and other healthcare providers. Although hard data is also lacking in this area, most centers agree to follow USDA guidelines and instruct avoidance of the following: unpasteurized milk, cheese, or juice; raw or undercooked eggs, meat, poultry, or seafood; raw seed sprouts; uncooked pate, meat spreads, and cold cuts; and cross-contamination when preparing food. When washed well, fresh fruits and vegetables can safely be consumed (Avery et al. 2009).

Monitoring

Full gastrointestinal nutritional autonomy is the most valuable and practical tool to assess intestinal graft function. This is accomplished by gradual weaning of PN while monitoring the clinical and biochemical nutrition parameters. Standard parameters to monitor on an ongoing basis are weight status, hydration status, and wound healing (Fryer et al. 2003). Serum immunosuppression levels can also be a reliable source to indicate that a patient is able to enterally absorb if the medication is given by mouth. The micronutrient status measured prior to transplant, including vitamin and trace elements, should be measured every 6 months after transplantation (Matarese et al. 2007). Even if patients can maintain themselves off PN, the ability of the bowel to fully absorb nutrients, vitamins, and minerals can still be limited.

Previously used absorption studies such as fecal fat excretion and d-xylose absorption studies have not shown to be accurate and reliable and are therefore not used as common practice to monitor graft function (Lennon 2010).

In order to monitor for acute intestinal rejection, an ileostomy is created at the time of transplant to allow access for ileoscopy and biopsy of the graft. The ileostomy is reversed 3–6 months after transplant, depending on the patient's anatomy posttransplantation.

Examples of the long-term complications posttransplant can include excessive weight gain or obesity, hyperlipidemia, and hypertension. These are partly due to the side effects of long-term immunosuppression drugs and poor eating habits. A healthy diet is encouraged during this phase. After surgery, some recipients discover the freedom to eat whatever they desire and find it difficult to comply with the suggested diet. Oftentimes, the recipients have developed poor eating habits over the years and endure lifelong issues.

Nutrition Management of Complications

Rejection of the intestinal graft is a common complication. Acute rejection is most common in the first 3–9 months and more prevalent when the visceral organ does not include the liver. At this time, there is no accurate serum test to determine function or predict rejection. Therefore, frequent biopsies are performed. Urgent endoscopy is needed for symptoms such as increased stool output, fevers, nausea, vomiting, low albumin, and elevated c-reactive protein. The endoscopy findings of acute rejection include short and blunted villi, edematous and friable mucosa, and ulcers. Other than the clear need for PN in the event of severe rejection, there are no guidelines to dictate nutritional care for the patient with rejection of an intestinal graft. This is an area that requires investigation, especially in regard to efficacy of enteral nutrition support during this event if a modular, such as glutamine, can be helpful for regeneration of enterocytes as the rejection is recovering.

Chronic rejection is also becoming more prevalent but not as easily identified or diagnosed. Symptoms of this are chronic diarrhea, abdominal pain, and graft malfunction with weight loss. In this case the biopsy may show mucosal and submucosal fibrosis and atrophy but a full thickness biopsy is needed to confirm the diagnosis (Avitzur and Grant 2010). Not only are there no nutrition recommendations but there doesn't seem to be a treatment for this other than retransplantation.

Other potential complications that can have effect on the nutrition plan can include dumping syndrome, small bowel bacterial overgrowth, pancreatic insufficiency, food allergies, hyperammonemia and renal dysfunction.

Conclusion

Intestinal and multivisceral transplant is a viable therapeutic option for patients with intestinal failure who have failed rehabilitation. Nutritional management is an essential component of post multivisceral transplant management, in the context of possible nutritional deficiencies and metabolic disturbances pretransplant. Close monitoring of nutrition indices at all phases of the transplant process should be done by a specifically trained dietitian as part of a multidisciplinary team. Although the majority of patients achieve nutrition autonomy and freedom of parenteral support, the optimal nutrition treatment after transplant has not been studied and requires an individual-based approach.

Cross-References

- ▶ Central Line Management and Intestinal Failure
- ▶ Modern Parenteral Nutrition
- ▶ Pharmacologic Considerations in Multivisceral Transplantation
- ▶ Psychosocial Issues in Intestinal Transplantation
- ▶ Recent Evolution of Gut Rehabilitation
- ▶ Visceral Transplantation: Current Trends and Long-Term Outcome

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Current Management of Intestinal Failure in Children

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Abstract

Intestinal failure is the complete loss of the alimentary tract's ability to absorb nutrients and is often the end result of progressive short bowel syndrome (SBS), defined as the malabsorption of nutrients secondary to either anatomical or functional loss of a significant portion of the small intestine. Common etiologies leading to anatomic (i.e., genetic or secondary to resection) and functional loss include necrotizing enterocolitis, volvulus, intestinal atresia, gastroschisis, as well as Hirschsprung's, chronic intestinal pseudo-obstruction, and inflammatory bowel disease, respectively. Maintenance of nutrition, managing risks of infection, and monitoring proper growth are vital components of caring for children with SBS. Parenteral nutrition (PN) is the initial standard of care that provides proper hydration, repletion of electrolytes, and provision of calories to enable normal growth. It also provides the gut opportunity to adapt and grow with the ultimate goal of regaining enteral autonomy. However, complications of PN including parenteral nutrition-associated cholestasis (PNAC), catheter-related bloodstream infections, intestinal bacterial overgrowth, and nutrient deficiencies must be managed. Persistence of intestinal failure can be managed surgically by autologous gut lengthening via longitudinal intestinal lengthening and tailoring (LILT) and serial transverse enteroplasty (STEP) operations in order to increase surface area for absorption and subsequent autonomy.

Keywords

Short gut syndrome · Intestinal failure · Total parenteral nutrition · TPN · Enteral autonomy · Enteral adaptation · Nutrient deficiencies · Small bowel transplantation · Longitudinal intestinal lengthening and tailoring · LILT · Serial transverse enteroplasty · STEP

Introduction

In the late 1800s, Koeberlé was the first to demonstrate that a portion of the small bowel could successfully be resected with patient survival. His pioneering work greatly advanced the state of abdominal surgery and opened the door to further advancements in surgical techniques and the field's understanding of the functioning of the small intestine. Throughout the twentieth century, various surgeons reported experiences with pediatric patients and survival among those with varying remnant lengths of bowel following resection. During this time investigators conducted experiments transplanting the small intestine in animals which later lead to Starzl's first successes with intestinal transplantation toward the end of the century. However it was in 1968 that Wilmore and Dudrick critically first described the use of parenteral nutrition (PN) for the growth and development of an infant with atresia of the small intestine. This child had severe disease from the ligament of Treitz to the ileocecal valve and experienced what would now be defined as intestinal failure following extensive small bowel resection for their disease. Normal growth and development occurred however following the intravenous administration of a solution replete with nitrogen, calories, and other essential nutrients, thus laying the foundation for the management of intestinal failure in children (Wilmore and Dudrick 1968).

Intestinal failure is the complete loss of the alimentary tract's ability to absorb nutrients. It is often the end result of progressive short bowel syndrome, defined as the malabsorption of nutrients secondary to either anatomical or functional loss of a significant portion of the small intestine. A variety of insults ranging from genetic atresias to mechanical obstructions necessitating surgical resection can reduce the length of small bowel available for normal absorption and subsequent growth and development. This chapter will

outline the causes of short bowel syndrome and intestinal failure as well as goals, strategies, and outcomes for the management of this challenging condition in the pediatric patient.

Etiologies and Demographics

The normal length of the small intestine increases during gestation from a length of approximately 100 cm around the 30th week, doubling to 200 cm at 35 weeks, and finally reaching lengths up to 300 cm for a full-term infant. Loss of too great a portion of the small bowel, typically thought of as an approximately 30% remaining length or less than 20–40 cm in most neonates, creates a situation where absorption is insufficient and will not allow for normal growth via normal enteral feeding.

The causes of short bowel syndrome and associated intestinal failure are largely secondary to either anatomical loss or functional loss of intestinal absorption. Anatomical loss occurs when either surgical resection of the bowel is undertaken or when congenital conditions lead to a physically reduced amount of small bowel present. Examples of these include resection secondary to necrotizing enterocolitis, volvulus, or gastroschisis and congenital short bowel or atresia, respectively (Squires et al. 2012; Cohran et al. 2017). Necrotizing enterocolitis is the most common cause of intestinal failure in the pediatric population, typically occurring in very low-birth-weight neonates (Neu and Walker 2011). Functional loss refers to a loss of the absorptive abilities of a normal length of small bowel. This may include malabsorption secondary to aganglionosis, chronic intestinal pseudoobstruction, or secretory diarrheas. Combinations of anatomical and functional loss leading to intestinal failure are not uncommon and may be present in up to 15% of such patients (Table 1).

Short bowel syndrome, while challenging to accurately estimate, is thought to occur in 3–5 patients per 100,000 live births in the USA (Squires et al. 2012; Cohran et al. 2017). Some data from European centers suggest that the condition is even more rare at 2–4 patients per 1,000,000. Due to great advances across the spectrum of pediatric care, from neonatal and intensive medicine to surgical therapies and nutritional support, young patients and their caregivers have able to enjoy enhanced prognosis following various insults to the intestines. Increased survival of some of these disease processes, especially those that necessitate surgical resection of small bowel, has likely led to an increase in the prevalence of short bowel syndrome and intestinal failure among neonates and infants.

Table 1 Common causes of short bowel syndrome in pediatric patients

Anatomic loss	Functional loss
Necrotizing enterocolitis	Hirschsprung's/small intestine aganglionosis
Volvulus	Chronic intestinal pseudoobstruction
Intestinal atresia	Secretory diarrhea
Gastroschisis	Inflammatory bowel disease
Trauma	Microvillus inclusion disease
Desmoid tumor	Tufting enteropathy
Inflammatory pseudotumor	Autoimmune enteropathy
Familial adenomatous polyposis	

Goals of Management

Maintenance of nutrition, managing risks of infection, and monitoring proper growth and development are the vital components of caring for children with short bowel syndrome and intestinal failure. PN is the vehicle that enables normal growth of these patients by allowing for proper hydration, repletion of electrolytes, and provision of calories. It also provides the gut the opportunity to adapt and grow with the ultimate goal of regaining enteral autonomy. However, PN is associated with a host of costs and complications, some of which are life threatening. These include but are not limited to parenteral nutrition-associated cholestasis (PNAC), catheter-related bloodstream infections, and intestinal bacterial overgrowth, all of which will be explored in a later section.

The likelihood of successfully weaning off PN and developing enteral autonomy has several important determinants including the length of residual intestinal length, the segments of intestine remaining (i.e., an intact ileocecal valve), and an underlying pathology of necrotizing enterocolitis rather than an intestinal atresia or gastroschisis (Spencer et al. 2005; Khan et al. 2015). For example, the cumulative probability of developing enteral autonomy in patients with greater than or equal to 50 cm of small intestine was 88% after 12 months and 96% after 24 months (Fallon et al. 2014). It is crucial to note that despite intestinal length being a more important determinant, it should not be used as the sole predictor of likelihood of achieving enteral autonomy. To highlight this point, studies have reported enteral autonomy with very short residual small intestine with one study reporting that 48% of patients with less than 20 cm of residual small intestine achieved enteral autonomy with a medial time of less than 24 months.

Regarding the segments of small intestine remaining, reduced duration of PN dependence has been demonstrated when the majority or all of the ileum is retained (Goulet et al. 2005). Additional benefits have been noted given the ileum's role in absorption of vitamin B-12 and bile salts. Impaired absorption of bile salts not only leads to steatorrhea but also increases the likelihood of deficiency in fat-soluble vitamins. Moreover, lack of an ileocecal valve lends way to small intestine bacterial overgrowth which compounds one's ability to absorb vitamin B-12 and deconjugate bile acids, thus worsening diarrhea and absorption of fat-soluble vitamins. Lastly, while the duodenum and jejunum are responsible for the vast majority of carbohydrate, proteins, and lipids, the ileum demonstrates unprecedented adaptation in compensating for absorption of these macronutrients when the proximal small bowel is anatomically or functionally lost (McDuffie et al. 2011; Tappenden 2014).

En route to the goal of enteral autonomy aggressive reintroduction of trophic feeds has been shown to be successful. Such physiologic nourishment allows for the natural growth of intestinal epithelium, activation of brush border enzymatic activity, and the upkeep of intestinal transporters, all of which help to maximize intestinal absorption and adaptation potential. Oral feeds have also been shown to stimulate epidermal growth factor and guard against complications of PN such as PNAC. In terms of the type of enteral feeds, breast milk has been associated with a decreased duration of PN, as have certain amino acid-based formulas. The immunoprotective benefits of breast milk, as well as the use of probiotics, may play a role in the avoidance of PNAC and infections for patients receiving both oral and tube feeds. For patients who may not yet be able to tolerate oral feeds, non-nutrient sucking can help avoid an oral aversion and may be an appropriate stepping stone to full-time enteral feeding.

Several overarching principles along with more specific protocols/algorithms have been documented to guide advancement of enteral feeding. Once trophic feeds are initiated via breast milk or amino acid-based formula, the volume of enteral feeds can safely be increased by 10–20 mL/kg/day as tolerated (Shores et al. 2018). A common threshold for enteral tolerance can be described as 2–3 mL/kg/hour of ostomy output or 10–20 g/kg/day of stool output (Gosselin and Duggan 2014). As such, if enteral fluid losses are less than this threshold, advancement in the rate of enteral feeds is appropriate. Conversely, output above this threshold suggests tolerance has been exceeded and warrants a reduction in enteral feeding rate.

Infected central venous lines are a feared complication of parenteral nutrition. Sepsis is a leading cause of mortality in this vulnerable patient population, with septic episodes occurring approximately 2 per 1000 central venous catheter days. Predictably, children who experienced a larger number of incidences of infection had worse outcomes relative to those with fewer infections. Prevention of sepsis is therefore paramount. Similarly bacterial overgrowth, defined as an increase or alteration in the bacterial floral of the small bowel typically greater than 10^5 colony-forming units per mL of fluid, presents a risk for infection or other complications such as D-lactic acidosis. Overgrowth can develop in the setting of

intestinal failure due to myriad reasons such as dysmotility and the loss of forward propulsion, alteration of anatomy, or a host of other changes to the integrity of the intestinal mucosa (Kaufman et al. 1997). Use of PN itself is another risk factor, and some studies have demonstrated that children who are PN-dependent are more likely to experience bacterial overgrowth than those who can be weaned from TPN (Kaufman et al. 1997). Given that these organisms represent hundreds of species of bacteria, it is challenging for antimicrobial therapy to be specific. Therefore, empiric treatment is preferred and must cover both aerobic and anaerobic bacteria. Some centers have suggested cycling of antibiotic therapy with regular courses of treatment interspersed with rest periods in an effort to reduce overall bacterial burden.

Finally, adaptation of the intestine, or the regaining of absorptive function following insult, takes place as the growth velocity and neurodevelopment of the patient are monitored. Recent data from the Pediatric Intestinal Failure Consortium shows that nearly two-thirds of pediatric patients diagnosed with intestinal failure will meet criteria for being underweight or having stunted growth or wasting at the outset. The process of enteral autonomy and attainment of good outcomes can therefore take up to years, even with careful attention paid to the management of nutrition and mitigation of risk factors for setbacks such as cholestasis or infection. Outcomes will also be explored later in the chapter.

Management Strategies

The management of intestinal failure in children may be considered in terms of three time periods: early, middle, and late term. Strategies in the immediate timeframe include focusing on preserving as much viable bowel as possible, establishing nutrition, and managing line access. The goal of any initial surgeries is to resect necrotic bowel and maintain as much viable bowel as possible. All areas of bowel that appear grossly normal should be preserved. Following resection of necrotic portions of bowel stomas may be utilized to allow time for healing. A number of types of stomas are appropriate, and following a period of growth and development, restoration of bowel continuity can be explored. There is no absolute timeline for when intestinal continuity should be reestablished and will be determined by the physiologic status of the child. This is typically measured by growth and development in the setting of weight gain. Following initial resections, "second-look" laparotomies may be completed in order to evaluate questionable bowel and check for signs of disease progression.

PNAC is a serious issue that occurs in approximately 50% of children and nearly 90% of neonates on PN. Due to the nonphysiologic and continuous nature of PN, bile output is decreased owning to alterations in normal gastrointestinal hormone signaling. This reduction in bile flow can result in static injury to the liver followed by hepatic steatosis, fibrosis, and eventually cirrhosis if not monitored for and corrected. Portal hypertension and liver failure occur in about 15% of patients and necessitate liver transplantation. Should PNAC be suspected, workup will require excluding other causes of liver malfunction and may include liver biopsy.

Establishing the source of nutrition via enteral feeds or TPN is paramount. TPN is the standard of treatment, and most patients with intestinal failure will utilize TPN for a period of time. Selection of type and composition of the TPN formulation is essential in delivering sufficient nutrients while also prophylactically mitigating inherent complications from the TPN itself. PNCA typically requires at least 2–3 weeks of TPN to develop. However, once on TPN steps to avoid PNAC should be instituted. Soybean lipid emulsions (i.e., intralipid) are the most common fat emulsions used in the USA, but new data suggests it may be associated with a higher risk of intestinal failure associated with liver disease (IFALD) (Diamond et al. 2017). Furthermore, when compared to patients who received soybean oil, patients who received olive oil or fish oil have a shorter duration of mechanical ventilation and shorter time to ICU discharge alive. As such, the use of Omegaven may be preferred as it is a fish oil-based emulsion, recently FDA approved

in 2018 that has been demonstrated to be hepatoprotective and anti-inflammatory. However, a drawback to a fish oil-based emulsion is that it provides reduced quantities of essential fatty acids (EFA), thus increasing the risk of EFA deficiency. Essential fatty acids in PN (notably linoleic and linolenic acids) play an essential role in neuronal development of neonates as they contribute to the general growth and health of cell membranes. As such, a new mixed oil emulsion consisting of soybean, medium-chain triglyceride (MCT), olive oil, and fish oil (SMOF) has been developed. A blinded randomized control trial comparing SOMF lipid to intralipid suggests a significant ability for SOMF lipid emulsion to prevent the progression of IFALD in infants (Diamond et al. 2017).

TPN cycling is another important strategy in reducing the risk of developing PNAC. For the neonate who can tolerate being disconnected from the IV and associated fluid shifts, parental cycling allows visceral protein stores to have the opportunity to build up; hyperinsulinemia may be reduced, and GI hormones may be more naturally released. In this setting gradual reintroduction of enteral feeds may be more successful (Friel and Bistrian 1997). Finally, it should be noted that in cases where multiple stomas are used, the distal mucus fistula should be "re-fed" with output from the proximal stoma in order to maximize absorption and gut function. Some centers advocate that enteral output should not exceed 50 mL/kg/d, but as long as the child is growing with a positive fluid balance and lack of perineal disease, higher output may be tolerated (Alkalay et al. 1995).

Central lines must be diligently cared for in order to maintain access and avoid the development of catheter-related bloodstream infections. Line locks utilizing ethanol have shown to be both bactericidal and fungicidal, while hydrochloric acid is another option that can disrupt biofilm buildup on central lines. Antibiotics are not recommended and may contribute to the development of resistance organisms.

Nutrient deficiencies in short bowel syndrome are also of concern particularly while weaning off TPN and once transitioned to full enteral feeds as the degree of intestinal adaptation is unpredictable. During this transition, up to 33% of children may have at least 1 vitamin deficiency and approximately 77% with a mineral deficiency (Yang 2011). Once transitioned to full enteral feeds, the prevalence and degree of nutrient deficiencies increases (Andorsky et al. 2001). The magnitude of risk and type of nutrient deficiency is associated with the portion of the small intestine that has been anatomically resected or functionally lost. The most common vitamin and mineral deficiencies, and those that should be monitored for routinely, include fat-soluble vitamins A, D, E, and K, vitamin B-12, as well as calcium, zinc, and iron.

Vitamins A, D, E, and K along with calcium are typically low-normal or deficient in patients with fat malabsorption related to TPN cholestasis or pancreatic insufficiency. Vitamin D deficiency is most common (68%) (Yang 2011), and when combined with calcium deficiency, patients are at significant risk for reduced bone mineral density and rickets. Risk of metabolic bone disease can be predicted by duration of PN-dependence (Demehri 2015). This risk is further increased when born prematurely or having used prophylactic bile acid resins such as cholestyramine. While on PN and once on full enteral feeds, monitoring for vitamins A, D (as 25-hydroxyvitamin D), E (as alpha-tocopherol), and K (as prothrombin time and international normalized ratio) is appropriate annually or every 3–6 months if the patient has evidence of deficiency, chronic liver disease or cholestasis, or is receiving enteral supplementation (Youssef et al. 2012). When on PN and once on full enteral feeds, complete metabolic panels should be ordered every 1–3 months and 6–8 months, respectively, to monitor electrolyte levels (i.e., calcium, phosphorus, and potassium) and hepatic functioning (Youssef et al. 2012). Prophylactic administration of liquid vitamin A, D, E, and K can be effective once TPN is weaned to less than 7 days a week. As such, 1 mL and 2 mL daily of aquADEK liquid can be given to children 0 to 12 months and 1–3 years old, respectively.

Vitamin B-12 deficiency is commonly seen after resection of the terminal ileum, the location at which it is absorbed. Patients with concomitant

small intestinal bacterial overgrowth have a less insidious onset of macrocytic anemia as the bacteria compete for B-12 and contribute to its deficiency. Given the body's hepatic stores of vitamin B-12, monitoring for B-12 deficiency is appropriate annually when on TPN and at the time TPN is discontinued with subsequent annual complete blood counts dictating the need for reassessment if a macrocytic anemia is discovered (Youssef et al. 2012). Replacement of vitamin B-12 can be accomplished intranasally, but it is most effective via a monthly intramuscular injection of 500 micrograms for children under 10 years old.

Zinc is another common deficiency among patients with SBS and typically presents as a chronic complication of SBS (67%) after being transitioned to full enteral nutrition (Yang 2011). Zinc and iron deficiency (37%) typically occur in this setting due to increased fecal losses and less commonly from decreased oral intake (Yang 2011). Zinc deficiency may manifest clinically as delayed wound healing or as acrodermatitis enteropathica in which they experience dermatitis, alopecia, and diarrhea. Labs typically show a decreased serum zinc concentration along with a low serum alkaline phosphatase concentration. It is reasonable to monitor zinc levels once at the time PN is discontinued and then annually (Youssef et al. 2012). Iron studies (iron, ferritin, TIBC, and transferrin saturation) can be monitored as clinically indicated while on PN; similar to zinc, once on enteral feeds, iron can be measured once at the time PN is discontinued and then annually (Youssef et al. 2012). It is important to note that concurrent measurement of C-reactive protein is recommended when measuring micronutrient deficiencies because the presence of an inflammatory state will falsely depress the zinc concentration and falsely elevate the ferritin concentrations. Replacement of elemental zinc can be accomplished via 2 mg/kg/day (American Academy of Pediatrics Committee on Nutrition 2014).

Electrolyte disturbances frequently occur as an early complication of SBS due to bowel length shortening and especially upon reintroduction or advancement of enteral feeds due to osmotic diarrhea. Patients with continuous watery diarrhea typically develop a hypokalemic metabolic acidosis without an anion gap and necessitate fluid and electrolyte replacement. Routine assessment of stool/ostomy output is needed to gage enteral tolerance to the current feeding regimen as well as to gage fluid status. Managing osmotic diarrhea can be accomplished by dietary modifications via slowing the enteral infusion rate, switching from bolus to continuous feeds, or by switching to a low carbohydrate high fat formula (Joly et al. 2009). Furthermore, switching to an enteral formula with greater than 50% of fat from MCTs is useful in patients with loss of the ileocecal valve whose diarrhea is secondary to malabsorbed bile salts. This provides benefit as MCTs are not dependent on bile salts for digestion and absorption. Concomitant pharmacological management via loperamide to slow gut transit thus enhances absorption of macronutrients and the uptake of sodium and water by 20–30% (Lennard-Jones 1994).

Medium-term strategies for intestinal failure management introduce the idea of autologous lengthening operations of the gut in order to increase the potential surface area for absorption. By increasing the length of whatever small bowel remains, there is an associated increase in autonomy, originally lost as the dilated and extended bowel lost its ability to propel fluid distally. The longitudinal intestinal lengthening and tailoring (LILT) and serial transverse enteroplasty (STEP) operations are the mainstays of gut lengthening (Abu-Elmagd 2015). Both are technically challenging surgeries that have shown good results. LILT and STEP demonstrate similar degrees of intestinal lengthening (approaching 70%), doubling of the percentage of enteral calories tolerated (30–60%), and TPN weaning (approximately 50%) (Frongia et al. 2013). Complications arise in about 10–20% of cases, the most feared of which are anastomotic leaks. STEP does offer some advantages over LILT, such as the ability to be performed on shorter segments of bowel or the duodenum and a somewhat lower mortality and progression to transplantation (Frongia et al. 2013). In evaluating patients for autologous lengthening, the potential repetition of these operations must be noted, for the risk of bleeding, infection, or surgical complications increases

with each and every subsequent surgery. There also exists a limited utility in increasing the length and autonomy of the gut – all such considerations of risks and benefits should be weighed in light of the child's physiologic status and overall prognosis.

As previously discussed the risk of bacterial overgrowth remains and should be guarded against with a high degree of suspicion and low threshold for instituting empiric antimicrobial therapy.

Complete enteral autonomy may be considered the ultimate long-term goal of the management of intestinal failure, and indeed some patients are able to ultimately achieve this. However, even with excellent medical and surgical management, approximately 15% of patients with intestinal failure will progress to bowel transplantation. All non-transplant interventions should be exhausted including intensive and aggressive monitoring and PN weaning as well as consideration for autologous lengthening procedures (DeLegge et al. 2007). Special considerations for referral of bowel transplant are warranted and include determining if a patient is a good candidate and which patients will benefit. There are several risk factors that may help identify a child who will progress to needing small bowel transplantation. In the child who develops progressive liver failure or refractory line sepsis, a small bowel transplant may be the only hope for cure. Additionally, if line access to multiple major veins are lost, typically defined as 2/4 in infants and 4/6 in children, or if under 10–20 cm of viable bowel is all that remains following resection, then transplant is again the only likely option. Loss of the ileocecal valve and persistent hyperbilirubinemia despite enteral nutrition also predict risk.

Patients who are referred early should be evaluated by a specialty center that will take these factors into account in light of the remaining length of bowel, its functionality, and overall prognosis. In the 25-year period from 1985 to 2010, over 1200 intestinal transplantations took place with overall survival rates just under 50%. More recently some specialized centers have demonstrated survival rates approaching 90% in the critical 12 months following surgery, owning to the advent of multidisciplinary care teams, sepsis-prevention techniques, and PNAC-prevention protocols (Hess et al. 2011).

Contraindications to bowel transplantation are similar to those for transplantation of other solid organs. Patients should be able to derive a tangible benefit and not suffer from profound and non-correctable neurological insult or other disease. There must be an absence of severe immunological disorders or other cancers, and the child should have sufficient vascular access for at least 6 months following transplantation. The risks and benefits of long-term PN versus transplantation should also be weighed. In the first 2 years following small bowel transplantation, the total costs of the operation and subsequent postoperative care generally outpace PN by a factor of two. Over time, however, PN costs can accumulate to a higher degree than surgery and might even reach as high as $500,000 in the first year of life. Overall survival at 5 years is approximately the same, however, likely due to the myriad risks involved with either course of action (Schalamon et al. 2003). For transplant patients on immunosuppression, the associated chance of rejection, infection, and cancers will always remain an issue, while patients on PN must avoid PNAC and other sources of morbidity and mortality.

Outcomes

Despite medical and surgical advancements that have led to the increased survival of patients with intestinal failure, the neurodevelopmental and quality-of-life outcomes for such survivors remain relatively unknown. A recent case series of 15 patients reported that 80% fell within the normal range on various measures of cognitive testing, defined as within two standard deviations of the mean on assessment. These patients had undergone intestinal resection at an early age for a variety of reasons and had a median remnant length of bowel of 18 cm. Those who did display neurodevelopmental impairment had significant associations with longer hospital stays, increased numbers of surgeries, and other risk factors such as prematurity (Chesley et al. 2016). Other studies

have suggested that neurodevelopmental outcomes in intestinal transplant patients may be worse than in those who undergo transplantation of other solid organs (Thevenin et al. 2006). For such patients who do develop cognitive delay or entities such as cerebral palsy, a decreased quality of life may be a concern, especially in the setting of parental stress. As these patients survive longer into older childhood, adolescence, and beyond, healthcare teams should focus on a multi-pronged approach to caring for both these patients and their caregivers.

While the majority of patients develop short bowel syndrome and associated intestinal failure following surgical resections, there are a cohort of patients who are born with substantially reduced lengths of bowel. One condition in particular, congenital short bowel syndrome, has been the focus of much research and serves as an example for the utility of genetic testing in families with multiple affected members. Mutations in two genes, *CLMP* and *FLNA*, have recently been identified as the cause of a recessive form of congenital short bowel syndrome, though their exact function and mechanism of causing truncated intestinal lengthening is still under investigation (Alves et al. 2016). Genetic screening in two unrelated families was successful in identifying *CLMP* variants in women, suggesting an X-linked pattern of inheritance. For families with a history of short bowel syndrome, there may be a utility in such screening for genetic counseling purposes.

For patients who progress to intestinal transplantation, the rates of individual and graft survival have improved over the past 30 years. However, overall conditional 5-year actuarial survival has not improved over time, recently plateauing at about 60% (Rivera and Wales 2016). For patients who survive the critical first year following transplantation, sepsis and chronic rejection remain the two most common causes of graft and patient death (Fishbein 2009). Immunosuppressive therapy leaves patients susceptible to a host of bacterial, viral, and fungal infections. Chronic rejection may subtly present itself as increased enteral output and can be confirmed with endoscopic bowel wall biopsies. Lymphoma is another common cause of death in posttransplant patients and is driven by EBV infection. Surveillance PCR and treatment with antiviral therapy such as ganciclovir has been successful in reducing the incidence of death from lymphoma.

Conclusion

Intestinal failure is a complex condition encountered in the pediatric patient who has usually suffered from another disease process resulting in the substantial decrease of small bowel available for adequate absorption, growth, and development. Surgical techniques that maximize the amount of native bowel and medical and nutritional therapy aiding in the recovery of small intestine following resection have been pivotal in increasing the rate of recovery from intestinal failure. Specialty centers that employ a multidisciplinary team of experts remain on the front lines for studies improving outcomes in the subset of patients who are unable to be weaned from PN or progress to bowel transplantation. Hope remains for these special pediatric patients and their caregivers and in the setting of further research will continue to grow.

Cross-References

- ▶ Causes of Short Bowel Syndrome in Adults
- ▶ Modern Parenteral Nutrition
- ▶ Nutrition Considerations in Multivisceral Transplantation
- ▶ Pediatric Causes of Short Bowel Syndrome

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Causes of Short Bowel Syndrome in Adults

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Abstract

In adults, short bowel syndrome results from a large number of etiologies, many of which will be discussed within this chapter. Short bowel syndrome can result from Crohn's disease, acute mesenteric ischemia, various forms of trauma, obstruction, and lastly, postoperatively. Crohn's disease leads to short bowel syndrome through the disease itself and the necessity of surgeries to mediate the intestinal damage. Acute mesenteric ischemia causes short bowel syndrome through reduction of blood flow but is not frequently observed. Similarly, trauma, such as blunt

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and penetrating trauma, can directly lead to short bowel syndrome through the damage of the gastrointestinal tract and organs in the abdomen. Obstruction, whether congenital, acquired, iatrogenic, etc., can contribute to progression to short bowel syndrome. With respect to obstruction, hernias in various locations, volvuli at different locations along the gastrointestinal tract, luminal obstructions possibly resulting from malignancy, and radiation-induced injury will be specifically addressed. Postoperatively, surgery in itself can place a patient at high risk for development of short bowel syndrome.

Keywords
Short bowel syndrome · Crohn's disease · Mesenteric ischemia · Bowel obstruction · Trauma · Postoperative complications

Introduction

Short bowel syndrome, a type of intestinal failure (Thompson et al. 2012a), is usually observed after significant bowel resection from various etiologies. Due to the shortened length postoperatively, patients experience electrolyte, fluid, nutrition, and protein imbalances from the decreased ability for digestion or absorption (Thompson et al. 2012a; Aggarwal et al. 2017). With such great importance being placed on the length remaining after surgery, there are many opinions on the length necessary to qualify for short bowel syndrome. With intestinal length as the most important factor of outcome (Thompson et al. 2012a), some sources dictate at least half of the small bowel should remain (Thompson et al. 2012a) while others recommend a length greater than 100 cm is needed to avoid intestine failure (Messing et al. 1999). Also, a terminal ileum, ileal remnant, and/or colon are more beneficial to the patient (Thompson et al. 2012a; Messing et al. 1999; Carbonnel et al. 1996). In more specific terms, patients were more likely to have poor outcome if they had jejunoileal anastomosis and a remaining small bowel length < 35 cm, patients with jejunocolic anastomosis and remaining small bowel length < 60 cm, and patients with an end jejunostomy and remaining small bowel length < 115 cm (Carbonnel et al. 1996, p.275). If the patient requires nutritional support for greater than 2 years, the patient is considered to have permanent intestinal failure (Thompson et al. 2012a).

After resection, intestinal adaptation is possible by hyperplasia of enterocytes to lengthen villi and by an increase in microvilli to increase the mucosal folds, which would increase absorptive surface area (Thompson et al. 2012a). After a longer period of time than gastrointestinal mucosal adaptation, intestinal muscle thickens and lengthens after the incident necessitating resection and usually requires more extensive surgical removal to develop (Thompson et al. 2012a). As motor activity is altered by surgery, extensive resection causes an abbreviated migrating motor complex cycle changes (Thompson et al. 2012a; Schmidt et al. 1996). Motor adaptation can occur with limited resection to regain normal intestinal motility, including institution of migrating motor complex cycling and decreased transit time, while smooth muscles contractility changes are limited (Thompson et al. 2012a).

In attempts to restore patient health, patients receive therapeutic rehabilitation, intended to increase intestinal function through behavioral, diet, and lifestyle changes, with the goal of a BMI of 20–25 kg/m^2 and correct nutrition (Thompson et al. 2012a). Surgical treatments can also be used for intestinal absorption rehabilitation after initial resection, where some strategies include tackling remnant preservation or surface area, enhancing motility and transplant (Thompson et al. 2012a).

Short bowel syndrome is due to many etiologies, which poses difficulty when discussing epidemiology. Because diagnoses of Short bowel syndrome may not be applied correctly and most statistics are based on home parenteral nutrition usage, the exact numbers of patients are unknown (Kelly et al. 2014). With respect to long-term patient survival, the majority of patient mortality is due to underlying diseases, illnesses, and complications of parenteral nutrition (Thompson et al. 2012a). Epidemiology may not be based on short

bowel syndrome but more likely on the underlying etiology of short bowel syndrome, which will be covered in the following sections.

Etiology of short bowel syndrome varies by age, but this chapter will focus on adult patients. For adults, some causes of short bowel syndrome include volvulus, ischemia, cancer, malignancy, and obstruction (See Table 1 for an additional list) (Thompson et al. 2012a). Thompson et al. stated that intestinal obstruction is the primary cause, especially with the predisposing factor of mesenteric ischemia potentially from mesenteric vascular disease (Thompson et al. 2012a). Thompson et al. conducted a 500 patient study where the most common causes included postoperative (35%), malignancy/radiation (19%), mesenteric vascular disease (17%), and Crohn's disease (16%) (Thompson et al. 2017). Aggarwal et al. found from their case analysis that a majority of short bowel syndrome cases were caused by mesenteric ischemia (Aggarwal et al. 2017).

Symptoms of short bowel syndrome are commonly noted to be steatorrhea, diarrhea, abdominal pain, dehydration, and malnutrition, but patients do differ in presentation, especially with varying possibilities of resection (Kelly et al. 2014). Symptoms are due to the decreased surface area for absorption and faster transit times through the intestines (Thompson et al. 2012a).

Many complications arise from short bowel syndrome including decreased absorption processes and increased transit time resulting in malnutrition (Thompson et al. 2012a). Metabolic acidosis due to bicarbonate loss through feces (Koda et al. 2013) and other metabolic derangements including electrolyte and fluid imbalances (Thompson et al. 2012a) are also dangerous complications. Due to poor absorption of vitamins, osteoporosis (Thompson et al. 2012a; Braga et al. 2015), osteopenia (Braga et al. 2015), and osteomala (Thompson et al. 2012a) are observed in patients with short bowel syndrome. In addition, other complications resulting from short bowel syndrome include hepatobiliary complications, such as cholethiasis and liver disease (Thompson et al. 2012a). Concerning hepatobiliary complications, necessity for cholecystectomy is exacerbated in obese patients (Thompson et al. 2012b). However, obesity may be a protective factor against hepatic steatosis (Thompson et al. 2012b). Furthermore, gastric hypersecretion, intestinal bacterial and flora changes, and renal conditions due to nonabsorbed ions in the intestine are also problems associated with patient recovery from the altered intestinal environment and length (Thompson et al. 2012a). More complications are summarized in Table 2.

Parenteral nutrition for short bowel syndrome poses its own difficulties, such as catheter infection, due to bacterial proliferation and stomas, and vascular access issues (Thompson et al. 2012a).

Table 1 Causes of short bowel syndrome

Infants	Necrotizing enterocolitis Intestinal atresia Gastroschisis Midgut volvulus
Children	Cancer Postoperative complication Trauma Motility disorders
Adults	Postoperative complications Irradiation/cancer Mesenteric vascular disease Crohn's disease Trauma Other benign causes

From: Etiologies of short bowel syndrome (Thompson et al. 2012a)

Table 2 Complications of short bowel syndrome and therapy

Catheter related	Infection Loss of vascular access
Hepatobiliary	Intestinal failure associated liver disease Cholelithiasis
Metabolic	Fluid and electrolyte abnormalities D-lactic acidosis Micronutrient deficiency Metabolic bone disease Osteoporosis and osteomalacia
Renal	Chronic renal failure Nephrolithiasis
Gastrointestinal	Gastric hypersecretion Small bowel bacterial overgrowth Changes in colonic flora

From: Short bowel syndrome complications (Thompson et al. 2012a)

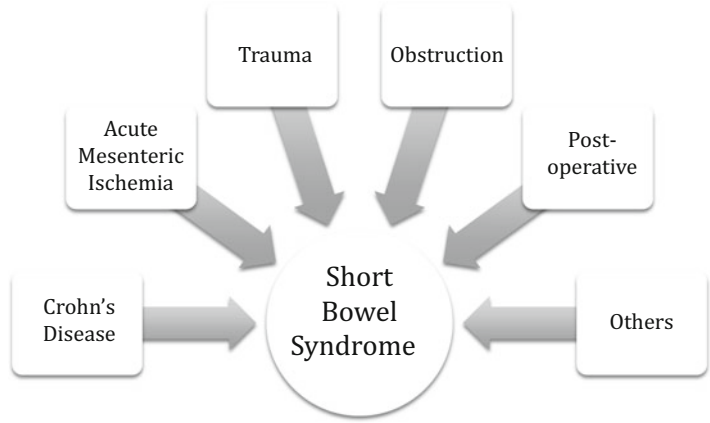

Fig. 1 Specific etiologies of short bowel syndrome to be discussed

Parenteral nutrition can also be a source of hepatobiliary complications, such as steatosis and gallbladder stones, in addition to the complications previously described for short bowel syndrome (Thompson et al. 2012a). Furthermore, a parenteral nutrition formula containing soybean oil lipid emulsion with long chain triglycerides may be associated with liver complications in this patient population (Weng and Chen 2015; Thompson et al. 2012a). Therefore, short bowel syndrome carries many potential morbidities, not only from the procedure and physically shorter intestine, but also from the therapy to aid patient survival.

Short bowel syndrome is the result of numerous medical conditions, diseases, and other occurrences of life. In the following sections, etiologies of Crohn's disease, acute mesenteric infarct, trauma, obstruction, and postoperative surgery will be discussed as causes of short bowel syndrome (Fig. 1).

Crohn's Disease and Short Bowel Syndrome

Crohn's disease is a chronic relapsing and progressive inflammatory disease of the gastrointestinal tract. It can affect any portion of the gastrointestinal tract from the mouth to the anus and is transmural in nature (Baumgart and Sandborn 2012). It affects approximately 1.3–5.3 out of every 100,000 adults. It is more common in females, Caucasians, and Jews (Sandler and Golden 1986). Thirty percent of Crohn's patients will have disease isolated to the ileum, 20% will have isolated colonic disease, but the majority will have ileocolonic involvement. As stated previously in this chapter, one series found Crohn's disease to be the fourth leading cause of short bowel syndrome (Thompson et al. 2012b).

Eighty percent of patients with Crohn's disease will require at least one operation for complications related to the gastrointestinal tract. Of these 16–36% will develop recurrent disease at 5 years and 28–55% will develop recurrent disease at 10 years. The mean time from initial diagnosis to the first operation is 6.4 years. Crohn's disease is a leading cause of short bowel syndrome (Thompson et al. 2003). One series found that 18% of patients with short bowel syndrome had Crohn's disease as the primary etiology. The overall risk of short bowel syndrome in patients with Crohn's disease is 5–12% (Thompson et al. 2003; Agwunobi et al. 2001).

There are a number of factors in the history and phenotype of patients with Crohn's disease that put them at higher risk for developing short bowel syndrome. As with all short bowel patients length of remaining intestine is probably the most critical factor in whether they develop short bowel syndrome. The median number of surgeries in Crohn's patient who developed short bowel syndrome was three, but the risk increases linearly with the number of surgeries. Patients operated on

for septic complications of Crohn's disease were at higher risk for short bowel syndrome as were those who underwent total colectomy, were given an ostomy, or had their ileocecal valves resected during an operation. Similarly, patients who had complications as a result of their surgeries for Crohn's disease were at higher risk for developing short bowel syndrome. The location of the disease was also a factor. Sixty percent of Crohn's disease patients who developed short bowel syndrome had ileocolonic disease. The incidence of Crohn's related short bowel syndrome also increased with duration of disease, earlier age at diagnosis, earlier age at the first operation, penetrating disease type versus structuring disease type, and steroid treatment (Uchino et al. 2012). Patients who smoked and/or had a family history of Crohn's Disease also were at higher risk for developing short bowel syndrome (Limketkai et al. 2016).

A significant number of patients with Crohn's disease will develop short bowel syndrome and may require small bowel transplant. Strategies to avoid the need for surgery with medical management and surgical techniques such as stricturoplasty and preserving bowel length in general to preserve absorbing mucosal surface, avoiding colectomy and ostomies, and preserving the ileocecal valve will reduce the risk of these patients developing short bowel syndrome (Jobanputra and Weiss 2007).

Acute Mesenteric Ischemia and Short Bowel Syndrome

Acute mesenteric ischemia is a more common cause of an acute abdomen in patients over the age of 75 than ruptured aortic aneurysm or appendicitis (Karkkainen and Acosta 2017). In one study the incidence of acute mesenteric ischemia in the general population was 12.9 in every 100,000 person years (Acosta 2010). Despite having been recognized as a disease entity for many decades, mortality for acute mesenteric ischemia remains high ranging from 50% to 80%. Therefore, due to the low survival, the actual number of mesenteric ischemia patients who go on to develop short bowel syndrome is also low (Acosta 2010; Sise 2014; Oldenburg et al. 2004; Bhandari et al. 2016).

The risk of developing acute mesenteric ischemia increases with age with males and females being at equal risk (Acosta 2010). Other risk factors for acute mesenteric ischemia include atrial fibrillation which is the most commonly cited risk factor, coronary artery disease, peripheral vascular disease, myocardial infarction, hypovolemic shock, congestive heart failure, digoxin use, a patient history of other embolic events, and hypercoagulable disorders. The etiologies of acute mesenteric ischemia are arterial embolus (40–50%), arterial thrombosis (20–25%), low flow or nonocclusive mesenteric ischemia (20%), and mesenteric venous thrombosis (10%) (Sise 2014; Oldenburg et al. 2004). In embolic disease the origin of the embolus affects the distribution of the area of ischemia. Cardiac emboli tend to lodge at the origin of the superior mesenteric artery thereby placing a large amount of bowel at risk. Most of the small bowel and one third to one half of the large bowel are at risk from emboli of this type. Superior mesenteric artery emboli lodge in the more distal proximal visceral branches or the mid-colic artery (Sise 2014). Patients with emboli due to atrial fibrillation had worse outcomes than all other patients, but the subset of atrial fibrillation patients that were on therapeutic anticoagulation tended to fare better (Bhandari et al. 2016).

Mesenteric venous thrombosis accounts for 1 in 5000 to 1 in 15,000 hospital admissions. Risk factors include hypercoagulable states, hematologic malignancy, vein wall injury, venous stasis, cirrhosis, and nephrotic syndrome. Anticoagulation with the addition of vasodilators is usually the initial therapeutic approach for these patients if signs of peritonitis are not present (Singal et al. 2013). Low-flow or nonocclusive mesenteric ischemia is usually seen in critically ill patients especially those with severe congestive heart failure, septic shock, hypovolemic shock, and vasopressor use. Vasopressin and Neosynephrine are both potent splanchnic vasoconstrictors and therefore patients receiving these agents for hypotension maybe at increased risk for bowel ischemia (Nygren et al. 2006; Bown et al. 2016).

The clinical diagnosis of acute mesenteric ischemia may be difficult. Laboratory studies such as lactate and white blood cell count might be elevated, but these findings are not specific to acute mesenteric ischemia. The initial visceral, nonlocalized nature of the pain and tenderness results in the "pain out of proportion to physical findings" that is classically described (Bala et al. 2017). Localized peritoneal signs usually do not occur until after frank infarction of perforation. Mesenteric venous thrombosis and arterial embolus or thrombosis have similar clinical presentations (Sise 2014; Singal et al. 2013).

CT angiogram is an effective, quick, and accurate way to diagnose acute mesenteric ischemia with an accuracy rate of 95.6%. Conventional angiography is more invasive and unlike CT angiogram not always immediately available (Ofer et al. 2009; Klempnauer et al.1997). An early index of suspicion and early diagnosis is essential to improving outcomes. When the diagnosis was made within 24 h of presentation, the survival was 50%, but if the diagnosis is made after 24 h the survival decreases to 30% (Oldenburg et al. 2004).

As stated above, mortality due to acute mesenteric ischemia remains high. Embolic disease mortality is 76% while arterial thrombotic disease carries a mortality of 83%. Nonocclusive mesenteric ischemia and mesenteric venous thrombosis carried 83% and 37% mortalities, respectively (Karkkainen and Acosta 2017). Because survival from acute mesenteric ischemia remains low, the overall incidence of short bowel syndrome in this population remains low as well. In one study, approximately 20% of those who survived their acute mesenteric ischemia developed short bowel syndrome. Another found that mortality was 62% and long-term parenteral nutrition was required in 31% of survivors. In this study, patients with embolic type ischemia initially have better survival than those with thrombotic type, but at 5 years the survival for both groups was only 20% (Edwards et al. 2003). The risk of recurrent ischemia is low especially if surviving patients are anticoagulated post event. However, long-term survival is also still low in anticoagulated patients with 50–70% of patients dying within 5 years of the ischemic event. The cause of death in these patients was usually cardiovascular in nature and not related to mesenteric ischemia (Klempnauer et al. 1997). Similar to other etiologies of short bowel syndrome, the incidence in the acute mesenteric ischemia population depends in part on the amount of small and large intestine left behind, the presence or absence of the ileocecal valve, and the presence or absence of an ostomy (Messing et al. 1999). Early diagnosis and intervention is essential to both survival and preservation of bowel length to prevent short bowel syndrome. Liberal use of CT angiogram, combined with early therapeutic anticoagulation where appropriate, noninvasive techniques, and early laparotomy with planned second-look laparotomy will maximize survival and the incidence of short bowel syndrome in those who survive (Sise 2014; Klempnauer et al. 1997).

Trauma and Short Bowel Syndrome

Another etiology of short bowel syndrome is trauma. Both penetrating and blunt force trauma to the abdomen can result in injury to the mesenteric vessels and/or bowel wall resulting in extensive bowel resections. Furthermore, concomitant injury to other digestive organs (stomach, duodenum, liver, gallbladder, and pancreas) can also influence nutritional outcome resulting in short bowel syndrome (Dabney et al. 2004). Additional extra-abdominal injuries in the polytrauma patient may also impact operative decision making, extent of bowel resection, and ultimate outcome. Severe trauma implicitly involves more than one organ and abdominal trauma usually effects a combination of solid organ, hollow viscus, and vascular injuries collectively contributing to the overall injury burden and threat to life (Nishida et al. 2004).

In a published review of short bowel syndrome after trauma, the multivisceral transplant team at University of Nebraska Medical Center reported its experience noting an 8% incidence of trauma as a primary etiology for short bowel syndrome (Dabney et al. 2004). Other series have similarly placed the incidence at less than 10%. Among the

adult intestinal transplant recipients at the University of Miami/Jackson Memorial Trauma Center, 15% are former trauma patients (Nishida et al. 2004). Trauma victims with short bowel syndrome are more commonly male and younger (majority under age 50 years) as compared to older females who constitute the patient population for most other etiologies of small bowel syndrome (Dabney et al. 2004; Nishida et al. 2004). The split is about even for penetrating versus blunt trauma as the cause, with gunshot wounds and motor vehicle collisions being the most common mechanisms of injury, respectively (Dabney et al. 2004). The majority of patients develop their disease as a result of injury to the mesenteric blood supply either from avulsion injuries of small branches in the mesentery or direct injury itself to the superior mesenteric artery and/or vein (Dabney et al. 2004; Frick et al. 1999; Nishida et al. 2004). For many of the patients, the massive bowel resections are performed at the index trauma laparotomy, although some need further significant resections at scheduled re-exploration/second-look operations too. Often patients need to undergo many subsequent abdominal operations for treatment of their injuries or management of complications related to their injuries, such as abdominal compartment syndrome, abscesses, fistulae, and adhesions or scar tissue that may require further resection potentially exacerbating or causing their short bowel condition (Dabney et al. 2004; Nishida et al. 2004).

Penetrating trauma from a projectile can cause numerous holes in bowel making it irreparable requiring resection. Generally this is more focal, however, leaving sufficient bowel to prevent short bowel syndrome albeit not necessarily the case (Dabney et al. 2004). Blast effect from penetrating trauma can cause further tissue ischemia and vascular thrombosis, often in delayed fashion, that can result in additional resection being necessary. Efforts to minimize anastomoses may also yield greater lengths of resection. Leaving bowel in discontinuity and planned second-look operations may help preserve questionably viable bowel by first permitting time for adequate resuscitation and restoration of optimal physiologic conditions before committing a patient to massive resection. Penetrating injury can also cause devascularization by directly disrupting the named vascular supply to large segments of bowel. SMA injuries are particularly rare and challenging injuries to control and reconstruct (Asensio et al. 2001). Short bowel syndrome is common in those who survive SMA injury. Venous thrombosis as may occur with SMV injury can also cause outflow obstruction yielding vascular congestion, bowel edema, and ultimately ischemia (Asensio et al. 2001).

Blunt force trauma can yield large mesenteric hematomas or mesenteric rents that can compromise bowel similarly. Lap seatbelts are particularly associated with this type of injury. Injury to the bowel mesentery does not often result in massive bowel loss but can cause focal or extensive devascularization requiring resection (Frick et al. 1999). Sudden application of extreme force can yield a significant change in intraluminal pressure that also results in perforation. Frequently multiple perforations are noted. Bowel wall hematomas can cause local injury leading to ischemia and perforation as well.

Early diagnosis of vascular injury is critical to preserving bowel, and resuscitative efforts are necessary to help avoid extensive resection resulting in short bowel syndrome from trauma. Intestinal and multivisceral transplantation offer options for treatment of intestinal failure as sequelae of severe abdominal trauma (Nishida et al. 2004).

Bowel Obstruction and Short Bowel Syndrome

Small bowel obstructions leading to short bowel syndrome are often mechanical in origin with a variety of etiologies. The major obstructive causes of short bowel syndrome in adults may be categorized as congenital, acquired, or iatrogenic and many may fall into more than one category. Hernias may be congenital, acquired, or iatrogenic. Volvulus may be acquired or iatrogenic, though rarely an adult midgut rotation with volvulus may present. Malignancy causes acquired obstructions as the lead point of volvulus, intussusception, kinking/

narrowing, and luminal obstruction. Post abdominal radiation adhesions may form, producing kinking, volvulus, or internal hernias long term. Type IV paraesophageal hernias may also torse within the hernia sac, creating long segment necrosis which can lead to short bowel syndrome.

Hernias are the third most common cause of small bowel obstruction and have the potential to strangulate large portions of bowel causing extensive necrosis and short bowel syndrome (Markogiannakis et al. 2007). Internal hernias are portions of bowel which incarcerate through congenital or acquired defects of the mesentery or adhesions. Mesenteric defects occur most commonly in the paraduodenal and pericecal areas but are also seen at the foramen of Winslow, intersigmoid, transmesenteric, or retroanastomotic spaces. Acquired causes of internal hernias are related to adhesions or new mesenteric openings made during the course of an operation, e.g., commonly Roux-en-Y gastric bypasses, pancreaticoduodenectomies, and ileal conduits (Hongo et al. 2011). Schneider et al. found in a retrospective review of 934 Roux-en-Y gastric bypasses that after multivariate analysis rapid weight loss defined as >90% of expected was the sole increased risk factor for internal hernias (Schneider et al. 2011). These patients present with nausea, vomiting, constipation, obstipation, and abdominal distention and pain. Patients may progress to peritonitis and sepsis as ischemia leads to acidosis and bacterial translocation, thus one must have a high index of suspicion in patients with a history of these procedures or those with rapid weight loss. CT findings include demonstration of the internal hernia and typical findings of obstruction with dilatation, distal decompression, air-fluid levels, or a closed loop obstruction. Special considerations in this population are chronic illness or malnutrition, vitamin deficiency if noncompliant with medications, and extensive prior operations with potentially hostile abdomens. Diaphragmatic hernias deserve mention as small bowel may herniate into the chest in the case of a Type IV paraesophageal hernia resulting in strangulation or volvulus. After resection and repair, the hernia sac must be completely excised and the defect in the hiatus must be repaired.

Abdominal wall hernias may occur at any area of muscular and ligamentous weakness. Congenital hernias are frequently through a patent umbilical ring, a weakened linea alba, or less frequently, the lumbar region. Acquired hernias may be present anywhere in the ventral abdominal wall, groin, flank, or pelvic spaces. Pelvic spaces hernias are those through the sciatic or obturator canals. Iatrogenic hernias include parastomal and incisional defects, especially in the midline. If there is fear of strangulation the hernia should not be reduced prior to the OR as this may lead to a larger incision to adequately run the bowel. Clinical signs of strangulated bowel are suspected in patients with pain, a form nodule at the hernia site, or overlying skin changes such as erythema. Peritonitis may be lacking as the necrotic bowel is wholly contained in the hernia sac. Vomiting and constipation may be absent if the hernia is a Richter's hernia involving ischemia of one side of the bowel only while maintaining luminal continuity, which can be clinically deceptive until extensive necrosis or perforation has occurred. Hernias may not always be palpable, especially in obese patients, thus a CT is often indicated though not necessary for diagnosis in the appropriate clinical setting.

On CT, bowel wall thickening, pneumatosis, free fluid, pneumoperitoneum, especially with portal venous gas may mandate operative exploration. Lactic acidosis and leukocytosis suggest progression to systemic illness and an increased likelihood of necrosis or perforation. Treatment begins with adequate resuscitation and correction of electrolytes. Antibiotics should be initiated if sepsis or signs of bacteremia are present.

Operative interventions should focus on removal of all necrotic bowel and restoration of continuity via primary anastomosis with diverting loop ostomy for select stable patients. Reperfusion injury may occur after restoration of blood flow and release of toxins from ischemic bowel back to the central circulation, thus clamping and resecting without attempt to detorse any necrotic segments, if unnecessary, is recommended. In unstable patients, leaving the patient in discontinuity for 24 h for resuscitation is a viable option, though every attempt at restoration should be

made as soon as possible. In the event of clear short bowel syndrome, the proximal alimentary tract should be decompressed via gastrostomy or gastrojejunostomy tube placement and wide intra-abdominal drainage.

Volvulus may be congenital in origin, in the case of adult malrotation or a Meckel's diverticulum, a true diverticulum. Acquired benign causes of volvuli may form secondary to adhesions from prior intra-abdominal inflammatory processes, or multifactorial causes in gastric and cecal volvulus. Iatrogenic volvulus may occur from twisted mesentery during a primary anastomosis, or prior adhesions leading to a lead point for torsion. Adult presentation of malrotation with volvulus is rare but is considered a surgical emergency if acute. Intermittent vomiting presents in 30% of patients followed by failure to thrive and bouts of abdominal pain. CT findings include abnormal course of the duodenum with a cecum in the left upper quadrant, reversed positioning of the superior mesenteric vessels, and a "whirlpool" sign due to mesenteric swirling. Surgical intervention is the removal of ischemic bowel and a Ladd's procedure of divisions of Ladd's bands, mesenteric widening, and replacement of the cecum and colon in normal anatomic position. Special consideration is the chronic malnutrition present in this population (Yanez and Spitz 1986). A Meckel's diverticulum is an adult cause of benign and malignant intussusception and volvulus, which can lead to widespread necrosis of the small bowel. The diverticulum is a remnant of the omphalomesenteric duct and is always on the antimesenteric side of the small bowel. Though present from birth, they may remain asymptomatic until adulthood.

Gastric and cecal volvulus causes seem to be multifactorial in nature. Volvulization occurs along the long organoaxial or short mesenteroaxial plane in gastric volvulus with other risk factors including age $>$ 50, diaphragm hernias, or phrenic nerve paralysis (Rashid 2010). Type IV paraesophageal hernias may include small bowel volvulus as well. Acute gastric volvulus is a surgical emergency and may lead to widespread necrosis of the bowel in a short amount of time. The etiology is typically secondary to another pathology like a paraesophageal hernia. Borchadt's triad of acute symptoms are nausea/vomiting, chest or abdominal pain, and inability to pass a nasogastric tube. Upright x-ray may show a large gastric bubble with air-fluid level in the upper abdomen or chest with a paucity of distal gas. CT is the mainstay of diagnosis. Patients will need resuscitation and electrolyte replacement from prolonged vomiting and immediate placement of a nasogastric tube. Surgical intervention relies on decompression, reduction of the organ(s) and detorsion of recoverable bowel, resection of the hernia sac and any necrotic bowel, reanastomosis, and repair of the diaphragmatic defect. Massive necrosis may dictate total gastrectomy or short bowel syndrome, necessitating resection with diversion and wide drainage, plus feeding access if possible.

Cecal volvulus may occur around its long axis or form a bascule, which is the upward folding of the cecum without mesenteric torsion. A congenitally mobile cecum may play a role due to failure of the ascending mesocolon to fuse with the posterior parietal peritoneum. Colonoscopies and pregnancy are also associated with cecal volvulus. Patients may present with chronic intermittent abdominal pain or acutely with abdominal catastrophe. Upright x-ray evidence of pneumoperitoneum mandates immediate operation, the pathognomonic "comma" and "coffee bean" sign of the medially superiorly displaced cecum only present in 25% of patients. CT is roughly equivalent with barium enema in diagnostic sensitivity of ~90% (Rosenblat et al. 2010). Cecal volvuli should all be operatively explored as ischemia may be present in up to one quarter of patients reduced with colonoscopy or barium enema, in addition to the risk of perforation. An ileocolic resection with colopexy or right hemicolectomy is the operation of choice. Unstable patients may have a cecostomy tube inserted but should rarely be needed when ileocolic resection and ostomy +/− mucus fistula are available options.

Luminal obstructions can be foreign objects, gallstone ileus, intramural lipomas, or other rare causes but in adults are most likely the cause of malignancy. Obstruction may take many forms,

from a lead point for volvulus or intussusception, to matting which may result in kinking or internal hernia, or tumor mass leading to intrinsic and/or extrinsic compression. The range of disease is also widely variable. Primary or secondary malignancies to the bowel can be of almost any origin in the body and may present with a single obstruction easily resected to an abdomen with an overwhelming burden of disease in which only palliation may be available, if that. Patients may present with obstruction as the first symptom of disease, or may present with known cancer and metastasis or prior intra-abdominal operation for malignancy. One third of obstructions in patients with prior abdominal operation for malignancy are due to benign adhesions (Tang et al. 1995). In fully resectable disease, the decision to resect and reconstruct is easy; however, the patient with significant intra-abdominal disease and a limited prognosis may not be an operative candidate at all or may only receive a palliative procedure. These may involve a bypass of obstructed bowel if there is no ischemia present or merely a venting gastrostomy tube. Even bypasses which functionally create short bowel syndrome or venting gastrostomy tubes may be preferable to the patient to allow them to eat. It is imperative that the operating surgeon have a goal of care conversation with patients with known local or metastatic intra-abdominal malignancy prior to surgery when possible. If widely necrotic bowel is present in the presence of extensive metastasis, the decision may need to be made either on the operating table or later in the intensive care unit to proceed with comfort measures only. If the patient was able to express their wishes pre-op, the best-case scenario, these directions may be followed through immediately. Aggressive malignancy is a contraindication to intestinal transplantation but may be performed for short bowel syndrome if cancer is of the gastrointestinal tract and pancreas, and is limited to the intra-abdominal cavity (Buchman et al. 2003).

Radiation-induced bowel injury is one of the less well-known indications for intestinal transplantation and may occur in as many as 40% of patients status post radiotherapy. Seventeen percent of patients with radiation induced bowel injury will require sugery for these injuries. Gynecologic, gastric, pancreatic, urologic cancers and sarcomas are all treated at some stage, either neoadjuvant or adjuvant, with radiotherapy which may make unresectable disease resectable or prevent loco-regional occurrence (Turina et al. 2008). The ileum is especially sensitive to radiation enteritis and effects of radiation may materialize years later and often require surgical intervention. Symptoms of radiation enteritis are ulceration, stenosis, or perforation in any volume of bowel. Surgery is indicated for obstruction from chronic stenotic changes when medical management fails or if bowel ischemia is suspected. Other radiation-induced bowel injuries include fistulae, perforation, bleeding, or secondary neoplasm. Patients are often chronically malnourished. Surgical considerations are based upon adequate or inadequate reserve of healthy bowel. Affected bowel may be resected if adequate length of bowel is left behind. Inadequate reserve from a radical resection or many small resections is more complicated. The focus of treatment may change to stricturoplasty if possible especially in patients with existing small bowel syndrome. In severe short bowel syndrome, metallic stents in addition to stricturoplasty can be performed. If operative findings show multiple areas of matting or strictures and resection is not feasible based upon the patient status, bypass may be utilized, especially if adequate reserve is achievable. If incurable disease is present then drainage is recommended with gastrostomy, jejunostomy, and/or ostomy until intestinal transplantation can be performed.

Postoperative Short Bowel Syndrome

In addition to all the etiologies discussed so far almost all of which involve a surgical procedure, short bowel syndrome may arise as a complication of elective surgical procedures as well. Thompson et al. found in their series that patients undergoing colectomy had the highest incidence of short bowel syndrome (38%), followed by hysterectomy (15%), appendectomy (9%), gastric bypass (9%), cholecystectomy (6%), gastrectomy (4%),

and ileoanal procedures (4%) (Thompson et al. 2005). In another manuscript, Thompson et al. looked at 500 patients with short bowel syndrome and found postoperative short bowel syndrome to be the most common etiology (Thompson et al. 2017).

In particular, patients undergoing bariatric procedures may be at higher risk for short bowel syndrome and over a longer period of time. McBride and colleagues reported that 4.1% of patients followed for over a decade after a bariatric procedure developed short bowel syndrome with approximately one quarter of short bowel cases occurring greater than 10 years postoperatively (McBride et al. 2006). Short bowel syndrome has also been reported after pancreaticoduodenectomy (Kim et al. 2002).

Conclusion

Short bowel syndrome can result from a number of etiologies including Crohn's disease, mesenteric ischemia, traumatic injury, bowel obstruction, and as a result of a complication from both emergent and elective surgical procedures not related to any of the above entities. The latter is especially true with bariatric procedures where the risk of developing short bowel syndrome extends well beyond the perioperative period. Regardless of the underlying etiology, short bowel syndrome is always the result of extensive surgical resection of small and sometimes large bowel. The need to resect the ileocecal valve or perform an ostomy places a patient at even higher risk for short bowel syndrome. Medical and noninvasive strategies should be employed whenever possible to manage Crohn's disease and mesenteric ischemia. Surgical strategies should be directed at avoiding or recognizing and repairing injuries to the mesenteric vasculature, avoiding ostomy creation, and preserving bowel length using modalities such as second-look laparotomy and stricturoplasty. All these measures will help decrease the risk to patients for developing short bowel syndrome requiring long-term parenteral nutrition and eventual small bowel transplant.

Cross-References

- ▶ Central Line Management and Intestinal Failure
- ▶ Recent Evolution of Gut Rehabilitation

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Pediatric Causes of Short Bowel Syndrome

Myles Dworkin and Reto M. Baertschiger

Contents

Abstract

Short bowel syndrome in pediatric patients can be a life threatening condition and is associated with insufficient intestinal absorptive function to sustain life without parenteral nutritional support. Causes of short bowel syndrome in children are multiple and can be secondary to congenital defects or acquired secondary to trauma inflammatory bowel disease, or other cause. The following are causes of short bowel syndrome in order of frequency: necrotizing enterocolitis, intestinal atresias, abdominal wall defects (gastroschisis and omphalocele), malrotation with midgut volvulus, Hirschsprung's disease, trauma, and Crohn's disease followed by rarer causes. The treatment of these conditions is surgical most of the time and aims at preserving as much

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bowel length as possible and allow intestinal adaptation. If this fails, small bowel transplantation may be necessary.

Keywords
Pediatric causes of short bowel syndrome · Necrotizing enterocolitis · Intestinal atresias · Gastroschisis · Omphalocele · Vanishing bowel syndrome · Malrotation · Mid-gut volvulus · Hirschsprung's disease · Crohn's disease · Trauma

Introduction

Short bowel syndrome (SBS) is a potentially life threatening condition in which there is insufficient intestinal absorptive surface area or absorptive function secondary to congenital or functional anomalies, or secondary to gastrointestinal resection and result in clinically significant malabsorption requiring specialized nutritional supportive therapy to sustain survival. SBS is the most common cause of the broader category of intestinal failure syndromes seen in patients who are unable to maintain sufficient nutrient and hydration statues due to pathology of the gastrointestinal tract (Wales and Christison-Lagay 2010). Precise epidemiological numbers concerning SBS are difficult to obtain due to the lack of a unified definition. Most recent studies base estimates on registries listing patients currently requiring **parenteral nutrition** (PN). Although an underestimation, these findings suggest a US population of at least 20,000 patients. Many studies utilizing data collected from Europe cite an incidence of two to three patients per million and a prevalence of four per million worldwide (Buchman et al. 2003). This number is distinctly divided into two classes based on adult or pediatric onset. Pediatric SBS is distinct from its adult counterpart and presents with a unique set of causes and complications. Although difficult to define due to the maturing intestinal system, a common definition of SBS in pediatric patients is the loss of at least 50% of small intestinal length from surgical resection or congenital defects (Spencer et al. 2005). Functional bowel length measuring less than this may lead to complications such as failure to thrive, chronic watery diarrhea, hepatobiliary disease, intestinal bacterial overgrowth, metabolic bone disease, as well as problems associated with PN such as central venous catheter related infections and PN associated cholestasis (Torres and Vanderhoof 2006). Short bowel syndrome is a leading cause of morbidity and mortality within the pediatric population with fatality rates around 25% (Cole et al. 2008). Extended hospitalization and expensive treatments create a large economic burden as the mean cost of care over a 5-year period is estimated to be $1.5 million per patient (Neu and Walker 2011). This chapter will examine the many etiologies of SBS within the pediatric population and describe them in more details (Table 1).

Table 1 Causes of short bowel syndrome and their incidence in children

Cause of short bowel syndrome	Incidence (%)[a]	Percent of pediatric intestinal transplantation (%)[b]
Necrotizing enterocolitis	35	15
Intestinal atresias	25	
Abdominal wall defects (gastroschisis and omphalocele)	18	24
Malrotation with midgut volvulus	14	14
Hirschsprung's disease	2	7
Other causes of SBS	6	19
Non-SBS causes		21

[a]Amin et al. (2013)
[b]Lao et al. (2010)

Necrotizing Enterocolitis

The most common cause of SBS within the pediatric population is **necrotizing enterocolitis (NEC)**. NEC represents a spectrum of intestinal inflammatory disorders primarily seen in

premature infants and children with extremely low birth weights. It may affect as many as 5% of all neonates weighing less than 1500 g and 10% of those weighing less than 1000 g (Patel and Shah 2012). NEC is not limited to preterm infants and a necrotizing enterocolitis-like disease may also be seen in children born at full term. This form of the disease is commonly observed in the perinatal period and associated with maternal drug use, congenital cardiac, and other anatomical defects, which result in decreased mesenteric blood flow and oxygenation causing hypoxic ischemic injuries.

NEC affects 5–10% of preterm neonates and has a mortality rate as high as 30–50% (Zani and Pierro 2015). Although the exact cause of NEC is unknown, multiple associated factors have been identified. The pathogenesis is currently thought to be an interplay between genetic predispositions, intestinal and immunological immaturity, microvascular factors, and abnormal microbial colonization (Neu and Walker 2011). Premature neonates with low birth weight develop an overactive inflammatory response and stress leading to NEC.

The signs and symptoms of the disease are primarily localized to the gastrointestinal system and may include feeding intolerance, abdominal distention, and bloody stools starting around the 8–10th day of life. These findings typically manifest in very distinct radiographic findings. Pathognomonic findings on imaging are pneumatosis intestinalis and/or portal venous gas although dilated bowel loops with air/fluid levels may also be seen depending on severity. Weakening of the bowel wall due to inflammation may cause transmural necrosis and perforations leading to free intra-abdominal air and peritonitis. An array of preventive approaches has been utilized in high-risk newborns to varying degrees of success. These may involve the use of enteral aminoglycosides, pre- and probiotics, glucocorticoids, arginine supplements, and anticytokine therapies. The best prophylactic effect, however, was achieved with slow introduction and advancement of enteral feedings of maternal breast milk. Unfortunately, these methods appear to be only minimally effective once NEC becomes clinically apparent. Medical therapy is typically instituted initially and consists of abdominal decompression, bowel rest, broad-spectrum antibiotics, and parenteral nutritional support. Surgery, however, is commonly required as up to 50% of children with NEC will develop advanced disease requiring intervention (Kosloske 1985).

The leading indications for surgical intervention are pneumoperitoneum, which indicates intestinal perforation, and continuous clinical deterioration despite maximal medical therapy (Robinson et al. 2017). There are currently two surgical options for the treatment of NEC: peritoneal drainage and exploratory laparotomy. Peritoneal drainage involves the placement of a Penrose drain within the peritoneal cavity. Normal saline is then used to irrigate the abdomen until clear fluid without signs of succus is obtained. If no improvement is observed within 24 h of initiation or if the child shows signs of deterioration, a laparotomy is typically performed. This involves a thorough inspection of the small bowel and colon for necrosis and resection of gangrenous or perforated bowel while maintaining as much bowel length as possible. The procedure may be completed using one of several techniques based on extent of disease and peritoneal contamination as well as hemodynamic stability of the patient. In focal disease with minimal contamination, defined as a single segment of gangrenous or perforated bowel, resection with a primary anastomosis can be performed. If the disease is multifocal, defined as diseased bowel appearing in multiple locations, a decision must be made as to whether or not to create a stoma. Placement of a stoma may be performed using either a single proximal enterostomy or multiple resections with multiple stomas. If a stoma is not placed, the Patch, Drain, and Wait (PD&W) or Clip and Drop-Back approach is utilized. The PD&W technique involves suturing the perforated bowel segments, inserting a Penrose drain in the lower abdomen, and long-term parenteral nutrition in addition to antibiotic use with observation. In the Clip and Drop-Back approach, necrotic bowel is resected and the ends of each segment are closed using titanium clips or staples. The patient is then observed for 48–72 h before clip or staple removal and anastomosis is

performed, potentially without the creation of a stoma. In up to 20% of patients, NEC *totalis* or panintestinal disease may develop. These patients have more than 75% of their intestinal tract affected. Surgical management of these cases is very difficult and bowel conservation is of paramount importance. Approaches are similar to those for multifocal disease, but resection of all diseased tissue is not recommended. Most strategies focus on proximal diversion without resection followed by second look laparotomies to reevaluate the viability of the bowel. The hope is that stomal placement may promote healing and reduce the need for resection (Castle et al. 2014). These patients, however, have exceedingly high rates of mortality and those that survive typically develop SBS. If NEC totalis is severe and involves the whole small bowel and colon, mortality is exceedingly high and some surgeons would offer comfort care at that time.

Peritoneal drainage and laparotomy are both viable options and the decision as to which to perform remains controversial. Over the past decade, several major prospective and retrospective trials have been undertaken to determine which method is superior. These studies have led to mixed results. A meta-analysis by Sola et al. showed that peritoneal drainage was associated with 55% excess mortality compared to laparotomy (Sola et al. 2010). This study, however, failed to take into consideration extent of disease at the time of operation. Recently, the Necrotizing Enterocolitis Trial challenged the hypothesis that the use of peritoneal drainage successfully stabilized pediatric patients prior to laparotomy. The findings from this trial showed that peritoneal drainage does not immediately improve clinical status in extremely low birth weight infants with bowel perforations, and it was not an effective definitive treatment strategy (Rees et al. 2008, 2010). Many other studies, such as Rao et al. (Rao et al. 2011) and Moss et al. (Moss et al. 2006), found that the type of operation performed did not significantly affect outcomes (Robinson et al. 2017; Neu and Walker 2011). Further studies are needed to fully define standard of care.

Long-term complications of NEC include intestinal strictures, due to fibrotic healing following inflammation, adhesive disease with risk of small bowel obstructions, and short bowel syndrome. Short bowel syndrome may result from either loss of function of a significant portion of the bowel or surgical resection. Approximately 42% of patients who suffered from NEC and required surgery will go on to develop SBS, whereas only 2% of those treated medically will. The surgical cases were associated with lower birth weights (<750 g), prior antibiotic use, and larger percentage of small bowel resection (Duro et al. 2010). Different surgical procedures were also associated with varying degrees of SBS. Peritoneal drainage was associated with a 4–9% risk of developing SBS while laparotomy was found to be between 10% and 46%, reflecting likely more severe disease. The creation of a jejunostomy and proximal diverting enterostomies was found to be significantly associated with SBS, while more distal stoma creations were not. A possible explanation for these findings was that more proximal resections were necessary secondary to more severe disease and resulted in shorter overall viable bowel length, even with a very conservative surgical approach.

Although patients with NEC have the greatest risk of developing SBS, patients with SBS due to NEC tend to have better outcomes compared to those who develop SBS for other reasons. The duration of SBS can be defined as the time period in which a patient requires parenteral nutrition. Thus, enteral autonomy is often viewed as the primary endpoint of the disease. A recent study found that 64.9% of patients with SBS due to NEC achieved enteral autonomy compared to only 29.2% of patients with SBS due to other causes. Furthermore, patients suffering from NEC were more likely to progress to enteral autonomy over several years indicating that remission was possible even after long periods of parenteral nutrition (Sparks et al. 2016). Despite the high mortality of NEC and its strong association with SBS, patients who develop intestinal failure have the highest likelihood of positive outcomes.

Intestinal Atresia

Intestinal atresia is the second leading cause of neonatal SBS accounting for up to 25% of all cases (Amin et al. 2013). Obstruction occurs due to a disruption in normal intestinal development and is most commonly seen in the small intestine with rates varying depending on location. Intestinal atresia is seen in approximately one in 5000–10,000 newborns; however, these rates increase depending on accompanying congenital anomalies. For example, duodenal atresia is commonly associated with chromosomal abnormalities such as Down syndrome. Approximately 2.5% of patients with trisomy 21 have duodenal atresia (Dalla Vecchia et al. 1998). The pathogenesis of atresia depends on the location and may result from either an abnormal developmental process or secondary to a fetal vascular accident or inflammatory process. Proximal duodenal atresias often reflect failures in organogenesis (Gharpure 2014). During weeks 6 and 7 of normal development, the endodermal epithelium of the duodenum will proliferate and occlude the lumen of the intestinal tract only to recanalize between weeks 8 and 10. Failure to restore patency can result in atresia.

Malrotation of the right pancreatic bud, known as annular pancreas, is another developmental abnormality that can occlude the duodenal lumen. Meanwhile, more distal atresias seen in the jejunum, ileum, and colon often result from a vascular disruption leading to ischemic bowel. The necrotic segment of bowel forms a blind-ending loop causing obstruction. There are many causes of ischemia including inflammatory processes, thrombo-embolic events, developmental defects, and familial causes (Seashore et al. 1987). Intestinal atresias have been classified in different types as shown in Fig. 1. Type 1 defines a simple web without mesenteric disruption. Type 2 defines two blind ends with intact mesentery, Type 3a defines two blind ends with a potentially large defect in the mesentery, Type 3b is the apple-peel type atresia, and Type 4 defines multiples atresia (string of sausages) (Grosfeld et al. 1979).

Type 3b is a rare, yet interesting, form of intestinal atresia known as an apple-peel atresia in which the intestine ends in a blind pouch while the distal segment wraps around the vascular supply in a spiral formation. This resembles an apple-peel on radiography.

Although morbidity from small-bowel atresia has increased over the last 15 years, mortality has dropped below 11% (Stollman et al. 2009). The leading complication is the development of SBS, which occurs in approximately 15% of children.

The presentation of neonates with intestinal atresia reflects the underlying bowel obstruction. Abdominal distention is typically noted, especially in more distal obstructions, and bilious emesis may begin within 24–48 h of birth. Intestinal atresias may be isolated or present with accompanying malformations such as cardiac, renal, vertebral, or distal intestinal anomalies as well as with cystic fibrosis, thrombophilia, and chromosomal aneuploidy. Diagnosis can be made using plain abdominal radiography. Duodenal atresias present with the pathognomonic double-bubble, while varying degrees of air-fluid levels and dilatation can be seen in more distal atresias. If diagnosis is uncertain, a contrast enema should be performed. In the last 20 years, prenatal ultrasound performed between 10 and 22 weeks of amenorrhea has improved significantly, and some atresias can be diagnosed or suspected prenatally. This is especially true for duodenal atresia, which is often associated with polyhydramnios, double bubble appearance of the foregut, and an intra-abdominal cystic lesion with dilated proximal bowel. More recently fetal MRI has also been used (Todros et al. 2001). Even with advanced imaging technology, distinguishing between fetal small and large bowel as well as the degree of dilation has proven to be difficult (Silva et al. 2015). Although there is no prevention of intestinal atresia, fetal screening should be done using the above-mentioned imaging techniques. Early diagnosis can help facilitate delivery in tertiary care centers, evaluate the fetus for associated malformations and may lead to improved treatment, and lowering morbidity and complications (Grosfeld et al. 1979). Isolated duodenal atresia is rarely associated with SBS, as long as the distal bowel is not affected.

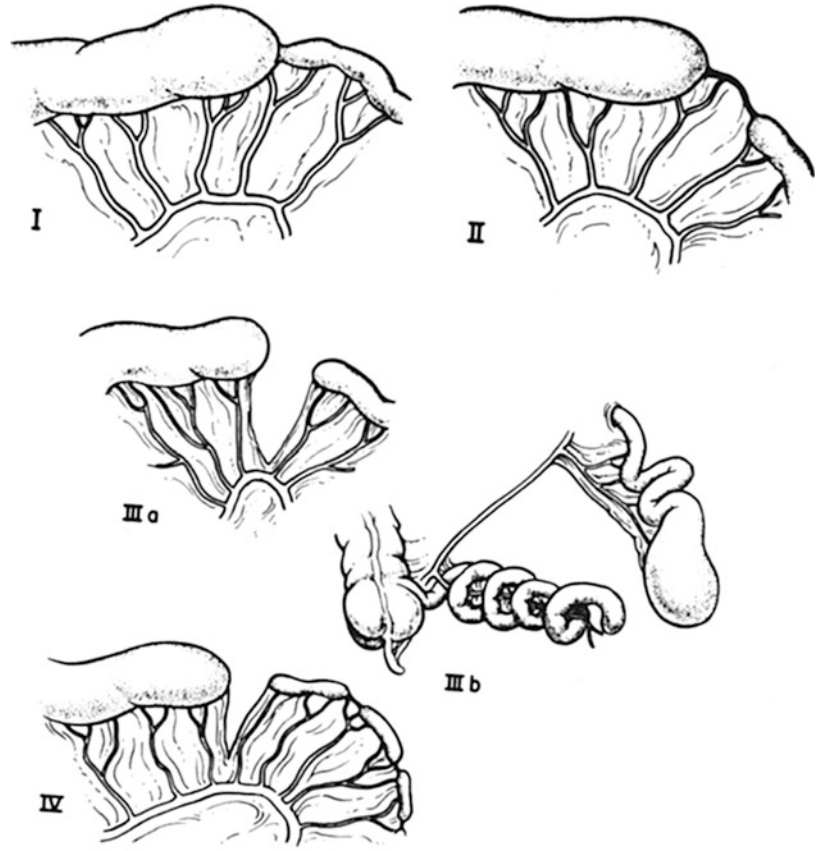

Fig. 1 Classification of intestinal atresias. (Reproduced with permission of *Journal of Pediatric Surgery*, Vol. 14, No. 3 (June), 1979)

There are no medical therapies available for newborns with small bowel atresia and surgery is the gold standard of treatment. The exact approach and timing of the operation depends on the location and cause of the atresia. For example, atresias due to prenatal **malrotation and midgut volvulus** should be considered emergent situations while developmental abnormalities may allow for more workup and 24–72 h delay. All neonates, however, should be initially managed preoperatively by withholding feedings, correcting electrolyte and fluid status, placing of a nasogastric tube to decompress the stomach, and providing broad-spectrum antibiotics (Hackam et al. 2015). Patients should also be evaluated for associated malformations including cardiac malformations, especially if duodenal atresia and clinical signs of Down's syndrome are present.

The objective of surgical treatment is to restore continuity of the bowel while preserving length and, if possible, the ileocecal valve. Resection of the ileocecal valve is associated with the need for twice the intestinal length to avoid SBS (Seetharam and Rodrigues 2011). The procedure of choice for a duodenal atresia is a duodeno-duodenostomy. This may be performed using either a right upper transverse abdominal incision or laparoscopy. The distal bowel is assessed during the operation and evaluated for secondary atresias. When present, dilation of the proximal duodenal pouch must be tapered in order to adjust the size discrepancy with the distal end. If the cause is annular pancreas, a bypass is created to avoid damage to the pancreatic ducts. For duodenal webs, a vertical duodenotomy is placed followed by excision of the web and transverse closure.

Surgical correction of jejunal, ileal, or colonic atresias is typically performed via laparotomy. Resection and anastomosis are the hallmarks of

the procedure and distal atresias should be ruled out. The degree of disparity between the proximal and distal segments of bowel may determine the exact technique, but most anastomoses are performed using an end to back technique along the antimesenteric border. The dilated proximal bowel will often have some degree of motility problems so resection of a distended segment should be performed. Tapering of this segment can also be carried out in the same manner as described above. If necrosis or ischemia is seen in the proximal bowel, an end ileostomy and mucus fistula can be created with delayed anastomosis.

The most serious common complication of these procedures is the development of SBS. This is most commonly seen in patients with multiple atresias often described as a "string of sausage" appearance (Type 4) or volvulus of the "apple peel" atresia type (Type 3b).

Abdominal Wall Defects

Gastroschisis and **omphalocele** are two additional common causes of short bowel syndrome presenting in the neonatal period. Although both are anterior abdominal wall defects, there are many important differentiating characteristics. Gastroschisis occurs due to a defect in the junction between the umbilicus and the abdominal wall leading to the herniation of intestines. This occurs in utero exposing the intestines to the amniotic fluid. Amniotic fluid exposure causes a defect in intestinal maturation leading to substantial abnormalities in motility (Nichol 2011). Meanwhile, omphalocele occurs due to a midline defect that results in the extrusion of viscera through the umbilical ring covered in a membranous sac made of peritoneum. During weeks 6 through 12 of development the intestines undergo a rapid expansion and must herniate into the extraembryonic celom at the base of the umbilical cord. Failure of the intestines to return to the abdominal cavity and rotate 270° leads to the formation of an omphalocele. These herniations may contain both intestinal and nonintestinal contents, most frequently the liver. Both omphalocele and gastroschisis are readily apparent at birth and are associated with intestinal pathology. However, overall morbidity and mortality associated with omphaloceles is much higher due to the high rate of associated malformations. Up to 75% of patients with an omphalocele have associated malformations compared to only 16% of gastroschisis (Stoll et al. 2008). Mortality for omphaloceles is up to 12–27% compared to less than 10% seen in gastroschisis. Gastroschisis, however, is more common with a recent increase in incidence to 2–6 per 10,000 newborns compared to omphalocele, which has an incidence of 2–2.5 per 10,000.

A rare and unique form of gastroschisis causes "vanishing gut syndrome." In these cases, the initial abdominal wall defect causing the gastroschisis spontaneously contracts or closes in utero leading to strangulation of the bowel. This is associated with mortality rates as high as 70% and potentially necessitates preterm delivery. If the fetuses survive, these children need TPN, and most of them will develop TPN associated complications such as intrahepatic cholestasis and liver failure (Dennison 2016).

Diagnosis is made either prenatally with ultrasound or at birth. The typical appearance of gastroschisis includes a full thickness abdominal wall defect with evisceration of the peritoneal content, including bowel, stomach, colon, more rarely bladder, ovaries, fallopian tubes, testicles, liver, and/or spleen. This typically occurs to the right of the umbilicus possibly related to the timing of involution of the right umbilical vein (Mandelia et al. 2013). Meanwhile omphaloceles may appear as a midline abdominal mass covered by a membrane protruding into the umbilicus. Most diagnoses, however, are commonly made during the prenatal period and allow for delivery at tertiary care centers with infrastructures for high-risk pregnancy. This has helped decrease mortality and has facilitated early closure of the defect. Once an abdominal wall defect has been diagnosed by ultrasound, the fetuses are followed closely for signs of distress as well as signs of thickened intestinal walls and mesenteric vascular compromise. As omphaloceles can be associated with midline defect, these fetuses also need a prenatal fetal echocardiogram.

Gastroschisis detection rates are between 70% and 72% by ultrasound. Characteristics include a normal appearing umbilicus with adjacent bowel herniation, wall thickening, and free floating intestines. The bowel will typically look distended with abnormal edges due to exposure to amniotic fluid. Omphaloceles can be detected by observing a midline mass herniating through the base of the umbilical ring. Wharton's jelly is present around the viscera, and the umbilical cord is usually attached to the tip of the mass. The umbilical vein can typically be identified. Magnetic resonance imaging may be used if diagnosis is difficult or to assess for associated malformations.

Although fetuses identified with abdominal wall defects should be delivered in a tertiary care facility, studies have found that there is no benefit to preterm or cesarean deliveries. Once delivery has occurred immediate surgical consultation should be obtained. The child should be placed on a radiant warmer to prevent hypothermia and IV fluids initiated to replace insensible fluid loss, that are increased given the exposed bowel, especially in gastroschisis. Omphalocele sacs should be covered in saline gauze. The intestines in gastroschisis should be evaluated for atresias and vascular compromise. The bowel should then be placed into a bowel bag with the newborn until surgical evaluation (Collin 2016). Surgical intervention is necessary in all cases of abdominal wall defects.

The surgical management of gastroschisis depends on whether the case is simple or complicated by intestinal atresia, perforations, or vascular compromise. Regardless of the classification, all patients will require at least some degree of total parenteral nutrition. The two main surgical options are the placement of a silastic silo with staged reduction or primary closure. Placement of a silo with gradual closure is performed when the bowel is felt to be too edematous and the abdominal cavity too small. This technique reduces the risk of abdominal compartment syndrome or bowel ischemia. The silo is suspended and gradually reduced over the course of several days. Once the bowel is fully returned into the abdominal cavity, the silo is removed and the defect closed. For patients with simple gastroschisis and limited bowel edema, an immediate primary closure may be performed. This involves reduction of the bowel and primary closure. The greatest concern with this approach is the development of abdominal compartment syndrome. This should be monitored by watching for signs of metabolic acidosis, respiratory compromise, hemodynamic instability, and increases in intraabdominal pressure. A silo should be placed if concerns arise. Complicated gastroschisis with atresias should be closed with a silo and the bowel repaired in a delayed fashion.

Regarding patients with omphalocele, a number of treatments have been described, including immediate repairs, staged repairs, or delayed repairs. The methods used depend on the size of the defect, accompanying malformations, and additional organs herniating through the abdominal wall, as well as surgeons' preferences. Small omphaloceles usually undergo immediate repair via primary closure. The omphalocele sac is opened followed by ligation of the umbilical vessels and urachus. The abdominal contents are then examined and manually returned into the abdominal cavity. Enlargement of the wall defect may be necessary. The fascia is then closed either primarily or with a patch if the defect is too large.

A staged or delayed approach should be conducted for larger omphaloceles or if complications arise with primary closure. Staged approaches involve excision of the sac and placement of a silo. The abdominal contents are slowly reduced over several days with close monitoring, prior to definitive fascia closure. This technique can also be applied for a ruptured omphalocele sac with significant extraperitoneal content (Islam 2014).

Omphaloceles are described as giant if they contain liver. If the omphalocele is very large or complicated by complex malformations, closure during the neonatal period may not be possible. In these instances, the sac is treated with topical antiseptic lotions (i.e., silver nitrate) to allow it to epithelialize and have the sac covered prior to closure. Primary closure may be considered 6–12 months later.

Survival for patients with gastroschisis is greater than 90% while those with omphalocele

range from 77% to 88% depending on coexisting malformations. Complications, however, are common and include sepsis, necrotizing enterocolitis, TPN related liver disease and line infections, as well as SBS. Vanishing bowel syndrome, atresias, tight closure, and the development of abdominal compartment syndrome are the leading causes of SBS in these patients. Outcomes are directly related to length of residual bowel with 86% survival in patients with greater than 15 cm of small bowel and higher rates of autonomous intestinal function in patients with greater than 10 cm (Thakur et al. 2002). However, patients with abdominal wall defects have high rates of intestinal failure compared to other causes of SBS and should be assessed for intestinal transplantation (Sala et al. 2010).

Malrotation with Volvulus

Malrotation with midgut volvulus is directly responsible for approximately 14% of SBS in newborns. Intestinal malrotation is a direct cause of rotational abnormalities during normal embryonic intestinal herniation and return into the peritoneal cavity. This may create a narrow-based mesentery with overlaying loops of small bowel that can be obstructed with aberrant bands (called Ladd's bands). Malrotation of the midgut is a fairly common occurrence with rates as high as one in 500 live births, but many will remain asymptomatic. Affected neonates may be seen in roughly one in 6000 newborns. Presentation of malrotation with midgut volvulus may occur at any age but 80% occur within the first month and 90% within the first year of life. The initial symptoms are signs of intestinal obstruction with bilious emesis. Gradual worsening conditions may present with peritonitis, acidosis, and shock if the condition is not recognized, given the vascular compromise of the bowel. The survival of children with midgut volvulus is greater than 80% but may be drastically lower in the presence of small bowel necrosis. The mortality in these cases depends on the extent of bowel involvement and reflects similar problems as other causes of SBS (Amano et al. 2014). Associated abnormalities can be seen with intestinal malrotation and these patients have a 22-fold increase in mortality. These related syndromes include duodenal atresia, abdominal wall defects, diaphragmatic hernias, situs inversus, and heterotaxia. Malrotation develops secondary to abnormal rotation of the midgut at approximately 10 weeks of gestation. It is at this time that the fetal intestines return to the abdominal cavity from the yolk sac and undergo a 270° counterclockwise rotation. Alterations in rotation cause a narrow mesenteric base and nonfixed superimposed loops of bowel leading to volvulus formation. The volvulus of the bowel happens most commonly with a clockwise rotation around the superior mesenteric artery as the main axis, thereby interfering directly with arterial blood supply. Malrotation can also be associated with displacement of the cecum and right colon and its peritoneal attachments known as Ladd's bands. These bands may compress nearby structures, such as the duodenum, causing obstruction (Fleischman 2016).

The most common presentation of malrotation with midgut volvulus is abrupt onset of obstructive symptoms. These include abdominal pain, distention, refusal to eat, and bilious vomiting. Severe hypovolemia is common and may be seen accompanied by the development of shock. Disease progression may lead to peritonitis with perforation or hematochezia due to ischemic necrosis. Symptomatic patients who are hemodynamically unstable should be urgently admitted for fluid resuscitation and surgery. Stable patients, however, should undergo diagnostic workup using various imaging techniques. A contrast enhanced upper GI series should be the first test performed. Studies have shown that UGI series have a sensitivity as high as 93–100% for simple midgut malrotation, but as low as 54% for the diagnosis of volvulus. Imaging may reveal a duodenum in a Z-shaped configuration due to peritoneal band obstruction, corkscrew-shaped if volvulus is present, or simply an abnormal position of the duodenojejunal junction. The cecum should also be visualized as it is displaced in up to 80% of patients with malrotation (Applegate et al. 2006). Classic signs of obstruction such as air-fluid levels within the intestines and ischemic

signs such as pneumatosis may also be seen. Small bowel follow-through may be used if findings are equivocal. Although less common, CT, MRI, and US imaging may reveal findings suggestive of malrotation and volvulus. However, these are much less frequently used in children because of their higher rate of radiation or need for sedation without a higher sensitivity compared to upper GI series. One highly sensitive and specific finding on US is the "whirlpool sign." This corresponds to a clockwise wrapping of the superior mesenteric vein and mesentery around the superior mesenteric artery and indicates a midgut volvulus (Rokade et al. 2011). Antenatal diagnosis may also be made using fetal MRI or US. Indications include a narrow mesenteric base, bowel dilation, and abnormal positioning of the duodenum and cecum.

Malrotation with midgut volvulus is a surgical emergency. Patients should be admitted for fluid and electrolyte resuscitation followed by an urgent laparotomy. After entering the peritoneal cavity, the surgeon identifies the volvulus and reduces it via a counter clockwise derotation. Viability is assessed after a time of reperfusion and necrotic tissue removed. Once this is addressed, **a Ladd's procedure** is performed in order to prevent the future formation of a volvulus. The first step is to divide the bands between the cecum and the abdominal wall as well as between the duodenum and the terminal ileum. The colon is then mobilized and placed into the left side of the abdomen. The duodenum is left on the right side. Lastly, the congenital bands along the SMA and SMV are divided in order to broaden the base of the mesentery. The appendix is typically also removed in order to avoid diagnostic challenges later in life and to allow formation of adhesions of the cecum in the left abdomen (Christison-Lagay and Langer 2014).

Complications following a Ladd's procedure are rare; however, recurrent volvulus can occur or small bowel obstruction can be seen later in life. The most significant problem in patients with malrotation and midgut volvulus is the development of SBS if the volvulus is not recognized and treated early enough. The incidence of SBS in malrotation with midgut volvulus is between 7% and 8% and depends on a number of factors such as time delay to surgery and size of volvulus. Mortality in these cases is very high and has been reported to be as high as 100% in some case series (Srinivas et al. 2017). This supports the importance of early detection and prompt treatment in all suspected patients.

Hirschsprung's Disease

Hirschsprung's disease, or congenital **aganglionic megacolon**, is the leading functional cause of SBS. It represents a motility abnormality in which neural crest cells fail to migrate to the distal segments of the bowel resulting in aganglionic segments in Auerbach's plexus and aperistalsis. In normal development, neural crest cell travel in a proximal to distal pattern. The majority of patients suffering from Hirschsprung's disease have distal recto-sigmoid aganglionosis. Approximately 5% of cases, however, may involve the entire colon and parts of the small intestine (Wall and Albanese 2014). Hirschsprung's disease is seen in one out of 5000 live births and is more commonly seen in males. The mortality rate is between 2.4% and 6% and depends on the extent of diseased bowel, the association with underlying disorders, and the development of enterocolitis. A number of associated malformations and syndromes may be seen. The most commonly associated syndromes include Down syndrome, familial dysautonomia (or Riley–Day syndrome), multiple endocrine neoplasia type 2, and Waardenburg syndrome (Amiel and Lyonnet 2001). Approximately 20–25% of patients will also have associated congenital anomalies. These include congenital cardiac disease, renal and genitourinary system defects, and ocular malformations. The failure of craniocaudal migration of neural crest cells results in dysfunction of the parasympathetic myenteric system of the distal bowel and thereby results in a functional bowel obstruction, as the musculature is unable to relax despite stimulation. Rare forms of the disease may also be seen in which cells are found in the correct location, but fail to differentiate properly or are destroyed. Familial factors are

also cited in 5–10% of cases with a strong genetic predisposition. The most common genetic abnormality is a loss of function mutation in the RET proto-oncogene. Other genes include those involved in the endothelin signaling pathway and the SOX10 gene.

Hirschsprung's disease most commonly presents during the newborn period, although mild cases may go undiagnosed for several years. Neonates typically present with features related to intestinal obstruction such as a failure to pass meconium within 48 h, abdominal distention, and bilious vomiting. A more specific finding includes relief of abdominal discomfort with rectal stimulation or enemas. This may elicit an explosive expulsion of gas and feces. These children also have high rates of enterocolitis. Ten percent of children may be diagnosed after the age of 3 and typically complain of ongoing constipation, distension, vomiting, and a failure to thrive. The initial diagnostic workup in the neonatal period includes a water-soluble enema that can be diagnostic and therapeutic to help express meconium. The caliber of the rectum and proximal distended bowel is assessed. The gold standard diagnostic procedure, however, is a biopsy of the rectal/intestinal wall. Rectal suction biopsy has recently replaced open procedures as it does not require general anesthesia in the newborn period and carries a lower risk of complications. It has a 93% sensitivity and a 98% specificity. The biopsy is taken proximally to the dentate line, and Hirschsprung's disease is confirmed by the absence of ganglion cells and the presence of hypertrophic nerves within Meissner's plexus. Other commonly used tests include anorectal manometry in older children with absence of anorectal relaxation upon stimulation, with a sensitivity of 91% and a specificity of 94%, and contrast enemas, with a sensitivity of 70% and specificity of 83% (De Lorijn et al. 2006). Anorectal manometry will show a failure of the intestinal wall to relax in response to distention. If a contrast enema is utilized, one may look for a transition zone or a change from normal to aganglionic segment. This will be recognized as a smaller caliber lumen in the diseased segment with proximal dilation. Abdominal radiography may also be used to look for signs of obstruction, but should be limited to prevent unnecessary radiation exposure in young children.

All cases of Hirschsprung's disease require surgery. This can be done through a number of operations with each producing similar outcomes. The goals of the procedure are the same regardless of technical approach. These include locating the transition zone from normal to diseased bowel, resection of the aganglionic component, and anastomosis of the proximal healthy bowel and distal internal anal sphincter. These procedures were used to be performed in a staged process in which a colostomy was created to allow decompression of dilated proximal bowel prior to resection and anastomosis. Depending on the level of the transition zone, some patients still need a leveling colostomy, especially for longer segment disease or ileostomy for total colonic disease. Currently, most surgeons perform procedures in a one-step pull through operation for recto-sigmoid disease and have achieved good results. The three major techniques include the Swenson operation, the Duhamel operation, and the Soave operation. These are typically performed laparoscopically to obtain a biopsy or with perineal approaches and pull through of the aganglionic segment through the anus. The Swenson operation involves dissecting the bowel within the pelvis and pulling it through until the healthy ganglionated intestine is proximal to the anus. These are then anastomosed via a perineal approach. In contrast, the Duhamel operation creates a side-to-side anastomosis between the aganglionic rectal pouch and healthy ganglionated bowel that is brought down after resection of diseased colon. The Soave procedure is performed with a submucosal rectal resection creating a muscular sleeve that is usually bivalved. The healthy bowel is then brought through this sleeve and anastomosed directly to the anus, 1 cm proximal to the dentate line.

Surgical correction of Hirschsprung's disease is fairly successful with minimal complications. The most common complications are postoperative enterocolitis, constipation, fecal incontinence, and anastomotic strictures (Hackam et al. 2015). Rates and severity of complications

depend on extent of disease. Total colonic aganglionosis has a higher risk of leading to the development of SBS. In fact, it is responsible for up to 2% of SBS in neonates and 7% of cases that require intestinal transplant (Amin et al. 2013; Lao et al. 2010).

Congenital Short Bowel Syndrome

Congenital SBS (CSBS) is an exceedingly rare form of SBS, as of 2008 there have only been 37 confirmed cases in the English literature (Hasosah et al. 2008). These patients have had a wide range of intestinal lengths and primary dysfunctions while the cause of SBS in these patients is unknown. As many as 96% have been found to have a malrotation in utero, but volvulus and bowel ischemia are very rare. Motility defects have been observed in some patients, but subsequent studies failed to reproduce these findings (Sansaricq et al. 1984). A familiar component has been identified; however, the exact mode of transmission is unclear at this time. While several studies have suggested an autosomal recessive pattern of inheritance (Sabharwal et al. 2004), new studies utilizing DNA analysis seek to find more specific causality. Genetic mapping in patients with CSBS have identified causative gene mutations likely linked to pathogenesis. For example, alterations to the Coxsackie and adenovirus receptor-like membrane protein (CLMP) are commonly found in CSBS patients. This is a membrane bound protein expressed in intestines of human embryos. It is responsible for tight-junction formation and loss of function mutations that have been shown to lead to shortened intestinal lengths both in humans and experimental zebrafish models (Van Der Werf et al. 2012). Many of these mutations are recessive. Some mutations, however, may be responsible for the disease in the heterozygote state. Furthermore, these truncating mutations within the CLMP protein were found to be associated with good clinical prognosis (Gonnaud et al. 2016).

Similarly to other causes of SBS, most patients present with diarrhea, vomiting, and failure to thrive. Signs of obstruction are also common. The lack of intestinal length leads to a malabsorptive state causing acidosis, hyponatremia, and hypokalemia in infants. Diagnosis is typically suggested using an upper gastrointestinal series with small bowel follow-through. Findings include a shortened duodenum, nonspecific dilation, and lack of jejunal or ileal differentiation (Palle and Reddy 2010). Exact diagnosis, however, is typically made at the time of surgical exploration (Hasosah et al. 2008). The mortality rate in patients with congenital SBS is 67.6% with an average life expectancy of 84 days. It should be noted, however, that the disease is very rare and many of these cases were reported prior to 1980 and several important advances in treatment have been developed since that time.

All patients require parenteral nutrition (PN) for survival. This caries the risk of several serious complications including high rates of sepsis. To prevent this, enteral feeding should supplement PN as early as possible. As for other causes of SBS, these newer approaches have led to bowel adaption and in some cases may have allowed for reduction and cessation of PN. Surgical options are available but limited. Bowel and combined intestinal and liver transplants may be necessary for survival.

Adolescent Causes

An important group of SBS patients that is often overlooked are those that acquire the disease during late childhood and adolescence. While there are many causes of SBS in this patient population the most common are **trauma**, neoplasm, **Crohn's disease, radiation enteritis**, postoperative complications, or other autoimmune and vasculitis-type diseases (Bruzoni et al. 2008). Although less frequently observed compared to the neonatal period, this cohort of patients require unique treatment strategies and individualized protocols. These patients require different approaches toward parenteral nutrition to meet different growth requirements. Both newly diagnosed adolescents and patients that were previously weaned off of nutritional support need long-term follow-up and additional therapy to prevent

failure to thrive. They have been shown to have exceedingly low vitamin D levels and pubertal delays, which require close nutritional monitoring for resolution (Miyasaka et al. 2010). Compared to neonatal SBS patients, adolescent cases also typically have different anatomical considerations. It is more common for newly diagnosed adolescent patients to have a preserved ileocecal valve, compared to the younger pediatric population. This is significant because preservation of the ileocecal valve and a preserved functional colon has been shown to decrease the dependence on PN (Bruzoni et al. 2008). The development of SBS must be considered when evaluating for gastrointestinal pathology in the adolescent population. Like for other causes of SBS, adolescent patients may undergo an array of treatment options including bowel lengthening and transplantation.

Trauma

Abdominal trauma necessitating bowel resection may occur at any age. Both blunt and penetrating injuries can cause damage to intestinal parenchyma and vascular supply. Although only roughly 1% of patients with abdominal traumas have significant injuries to the small bowel, 93% of small bowel damage may require resection (Dabney et al. 2004). These patients often have diffuse injuries requiring extensive resection/repair at presentation. The presence of additional injuries greatly influences the outcome of these patients with rates of mortality and morbidity related to the extent and severity of the initial trauma. The viability of the superior mesenteric artery and vein is the primary determinate for the development of SBS, as direct damage to the bowel wall tends to be more focal in nature reducing the need for extensive resection. Anywhere from 5% to 38% of trauma patients with SMA injuries may develop SBS due to widespread necrosis. Special consideration should be provided during the time of repair to maintain the ileocecal valve. As mentioned earlier, preservation of the ileocecal valve is associated with reduced dependence on PN. Other strategies for minimizing the risk of SBS is early diagnosis of vascular injury and the use of second look procedures to determine the extent of damage. SBS in trauma patients accounts for approximately 15% of intestinal transplantations (Nishida et al. 2004).

Crohn's Disease

Crohn's disease (CD) is an immune-mediated inflammatory bowel disease. It may affect any part of the gastrointestinal tract from the mouth to the anus. Common characteristics specific to CD include skip lesions, granulomatous transmural inflammation, rectal sparing, and terminal ileum involvement. The disease is commonly associated with fistulas, abscesses, and strictures (Friedman and Blumberg 2014). As of 2009, the prevalence of CD in the pediatric population (age <20) was 58 per 100,000. There are roughly 565,000 patients currently diagnosed with the disease in the United States and 38,000 are children (Kappelman et al. 2013). Exact rates of mortality vary, but recent meta-analyses have concluded a slight but significantly higher overall mortality compared to the general population. This is most common due to malignancies (Duricova et al. 2010).

CD may affect a wide range of locations within the gastrointestinal tract, and symptomatic presentation is determined by the site of pathogenesis. The most common location is the terminal ileum. Symptoms of ileocolitis include recurrent episodes of right lower quadrant pain, diarrhea, and hematochezia. Weight loss and low-grade fevers are common. Proximal small bowel involvement is common leading to loss of digestive and absorptive surfaces. This may manifest as malabsorption, including diarrhea, steatorrhea, electrolyte abnormalities, and nutritional deficiencies. Untreated inflammation can cause fibrosis and stricture formation leading to obstruction. Other complications from this include fistulization. A rare but severe evolution of CD is toxic megacolon. This involves nonobstructive dilation of the colon accompanied by systemic symptoms of sepsis such as fever, pain, and shock.

Diagnosis is typically made using mucosal biopsies. Findings include noncaseating granulomas in all layers of the bowel wall, submucosal lymphoid aggregates, skip lesions, and transmural inflammation. Patients may also undergo CT or MR enterography to explore small bowel involvement. Pathology may present as ulcerations, strictures, bowel wall thickening, and fat stranding. Capsule imaging has also been implemented to help with diagnosis (McQuaid 2018). Although laboratory findings are variable, common abnormalities include elevated C-reactive protein, anemia, leukocytosis, and hypoalbuminemia. The initial treatment for CD involves anti-inflammatory medications. Commonly used therapies focus on corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs), such as 5-aminosalicylic acids, to control symptoms. Recent innovations in long-term management have shifted toward biologic therapy, including the use of humanized recombinant antibodies against TNF-alpha or an alpha-4 integrin subunit to control the inflammatory cascade. Drugs such as infliximab, adalimumab, certolizumab, and natalizumab have been shown to be very effective at preventing recurrent symptoms (Bandzar et al. 2013). Despite the creation of new medical therapy, up to one third of patients will require an intestinal surgery within the first 5 years of diagnosis and 50% will require at least one surgical procedure within their lifetime (Hovde and Moum 2012).

Indications for surgery include symptoms refractory to maximal medical therapy, intra-abdominal abscess, massive bleeding, fistula formation, malignancy, and intestinal obstruction. The most common surgical procedure in CD patients is an ileocecal resection. Stricturoplasty and endoscopic dilation of short strictures may also be performed. Although effective at symptomatic control, disease recurrence is common. As many as 26% of patients may experience relapse within 5 years (Lewis and Maron 2010). The most common complications include the formation of fistulas and abscesses. The rate of multiple resections ranges from 22% to 33% and increases the risk of the development of SBS (Krupnick and Morris 2000). Predictive factors for the development of SBS include younger age at diagnosis, younger age at first surgery, ileocolonic involvement, and perianal disease. Widespread pathology is also a risk factor for the development of SBS in children with CD. Patients suffering from CD have a 17% incidence of SBS that is correlated with extensive primary disease (Walker-Smith et al. 2009). Minimizing surgical interventions and intestinal resection as well as the development of stricturoplasty techniques have decreased the incidence of SBS in patients with CD (Jobanputra and Weiss 2007).

Surgical Intervention

New forms of treatment for SBS are continuously being studied. Advances in the field of PN have allowed for longer life expectancies. Early enteral feeding and the development of more elemental formulas have allowed the development of enteral autonomy. Despite this progress, surgical treatment is often required. The two main strategies include bowel lengthening and transplantation. Lengthening is typically performed by either **longitudinal intestinal lengthening and tapering** (LILT) (Bianchi 1997) or **serial transverse enteroplasty** (STEP) (Kim et al. 2003). The LILT procedure was originally described by Dr. Bianchi in Manchester, UK. This involves dividing the proximal dilated bowel longitudinally and creating two lumens. These loops are then joined through end-to-end anastomosis. STEP was initially described by Dr. Kim in Boston, MA, and is performed by making transverse cuts perpendicular to the long axis of the dilated bowel using a stapling device (Tavakkoli et al. 2015). Both techniques associated with multidisciplinary intestinal adaptation programs have been effective at increasing enteral autonomy and reducing the need for transplant procedures (Almond et al. 2013). Transplantation is still commonly performed with 1- and 5-year patient survival rates of 95% and 77%, respectively (Mazariegos et al. 2009). The most common cause leading to transplantation is gastroschisis, followed by volvulus and NEC.

Conclusion

SBS is a devastating disease, which often affects a vulnerable pediatric population. Children may develop the disease at any time and its etiology is correlated with age of onset. Neonates are the most commonly affected subset of patients. Within this population about 35% of cases are due to NEC, 25% due to intestinal atresia, 18% due to abdominal wall defects, 14% due to malrotation with volvulus, and 2% due to Hirschsprung's disease. Although rare, children may also be born with a congenital short bowel. Older children and adolescents may also develop SBS. This group of patients is often overlooked due to infrequent presentation, but requires their own unique treatment approach. Exact epidemiological numbers are difficult to determine, but causes include trauma, neoplasms, Crohn's disease, radiation enteritis, autoimmune disease, and postoperative complications. Despite the various etiologies that may cause SBS, presentation is similar allowing for early recognition and diagnosis. New forms of treatment involving PN, medical therapy, and bowel lengthening procedures have created a more recent concept of intestinal adaptation and helped to reduce the morbidity and mortality of pediatric SBS.

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Index

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