REPORT OF THE FIRST COMPREHENSIVE RENAL REPLACEMENT THERAPY PROGRAM IN GUYANA, SOUTH AMERICA

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Introduction

The needs and expectations of the developing countries have grown in an increasingly globalized world. There is a clear need to develop specialized health services in addition to primary care. Exactly how such healthcare should be paid for, via private insurers, government subsidies, or a mixture of both, is a subject of great debate.[1] One such form of acute/chronic care is renal replacement therapy (RRT), which is non-existent in developing countries and the unfortunate fact is that a diagnosis of end stage renal disease (ESRD) is tantamount to a death sentence.[2] This was most certainly the case in Guyana, South America, in 2008, when we began our efforts there to deliver RRT. We herein, describe the summary of 14 medical missions to Guyana with emphasis on logistics and outcomes of our public-private partnership. This model is now being extended to the CARICOM, a grouping of 20 countries in the Caribbean basin.[3]

Incidence of Kidney Failure in Developed vs. Developing Countries

The incidence of kidney failure in the developed countries has been well-documented. In the US, the prevalence of chronic kidney disease (CKD) was found to be 13.1% between 1999 and 2004.[4] Between the US and Europe, it is estimated that some 10% of the adult population is affected by kidney disease, with nearly a 1 million requiring some form of RRT.[5] As for the particular method of RRT that a patient receives in Western medicine, most begin their treatment with some form of dialysis, after the establishment of either vascular or peritoneal dialysis access. Kidney transplant is the most cost effective form of RRT, leading to improved quality of life with clear survival advantage over dialysis, to the point that physicians encourage pre-emptive transplantations in lieu of initiating dialysis.[6]

The situation in developing countries is more dire. Due to socioeconomic and logistical factors, patients rarely have access to any form of RRT. In India for instance, even conservative calculations point to a 100,000 new cases of ESRD per year requiring RRT. With most dialysis centers located in inaccessible metropolitan settings, many rural Indian patients are not treated and succumb.[7] In many other Asian countries as well, the incidence of ESRD is rising rapidly due to the rise of other risk factors, such as diabetes and hypertension.[8] By the end of 2002, over 300,000 patients in Asia were reported to be on dialysis.[9] In Guyana, South America, the incidence of new hypertension and diabetes cases is approximately 10,000 and 8,000 cases per year, respectively. When we began our intervention there in 2008, there were 200 known cases of Guyanese patients requiring dialysis.[10,11] In addition, it is important to note that all of these numbers pertaining to developing countries are most likely underestimated due to absence of national registries to collect this information.

Cost of Renal Replacement Therapy in Developed vs. Developing Countries

In the United States, the overall cost of managing a patient with CKD and that of hemodialysis (HD) specifically has been estimated to be USD $22,000 and $88,000 per patient per year, respectively.[12] The cost of a kidney transplant in the U.S. can surpass a quarter of a million dollars.[13] The cost of HD in developing countries such as India, Indonesia, China, and Brazil can range from USD $5,000 to $7,500 per patient per year.[14] The senior author and the philanthropist made a couple of preliminary fact finding visits to Guyana in early 2008. We found that there were only 3 dialysis units for a population of approximately 1 million. The cost of HD per session in Guyana was approximately USD $200 per dialysis session. Assuming a thrice weekly regimen, the yearly cost for HD per patient in Guyana would be USD $31,200. In a

country where the gross national income per capita was USD $2,900 in 2010,[15] with little state support and no viable insurance system, patients have little options and often die from kidney disease.

Networks

Our efforts in Guyana began with the establishment of a key network, comprising of four entities: (1) philanthropic Guyanese-Americans; (2) U.S. transplant physicians; (3) the Guyanese government; and (4) Guyanese physicians. The Guyanese-American community was instrumental in helping us understand the socioeconomic conditions of their country. The majority of the funding (transport and local stay for the 5-member team) was provided by Mr. George Subraj from Queens, New York. The U.S. transplant professionals lead by Dr. Jindal consisted of Transplant Surgeons, a Nephrologist, an OR nurse, a dialysis nurse and an Anesthesiologist from the Walter Reed National Military Medical Center (WRNMMC, Bethesda, Maryland) and Drexel University (Philadelphia, PA).

The Guyanese government played a significant role in facilitating this nascent RRT program in their country. They provided the use of the hospital (Balwant Singh Hospital, Georgetown, Guyana), provided dialysis fluid and anti-rejection medications at no charge. The local staff identified patients, performed the necessary workup and provided follow up. They scrubbed in the OR and participated in post-operative care. It was through this network that we were able to provide quality healthcare to Guyanese patients with CKD and ESRD who would have otherwise died.

Results of the First Peritoneal Dialysis Program in Guyana

We introduced peritoneal dialysis (PD) to the country. We initiated the program by appropriate patient selection and performed 17 catheter placements in the first phase over 1 year. This was accompanied by teaching and follow up by Skype clinics. Box 1 displays the demographics, cause of kidney failure, complications and outcomes. We treated 17 patients; the mean age of this patient group was 43.6, with a range of youngest 8-years old to eldest 76-years old. There were 5 deaths, 2 younger patients, 8- and 15-years old, died approximately 2 weeks after PD catheter placement, due to acute kidney and multi-organ failure. The other deaths were attributed to co-morbidities or unknown causes. Other complications included 2 conversions to HD that became necessary due to inadequate clearance, 1 instance of PD catheter malfunction that was successfully corrected, and 1 instance of PD catheter exit site infection (that failed initial treatment with antibiotics, but was surgically corrected). Aside from these negative outcomes, these patients did well with their self-administered PD regimen. Of note, in 4 cases, the PD regimen served as a successful bridge to kidney transplantation. These patients would have likely died before obtaining the transplant, had it not been for this bridge. We continue to perform PD during our visits and follow these patients in conjunction with our colleagues in Guyana.[16]

Results of First Vascular Access Program in Guyana

We introduced the concept of vascular access for dialysis to Guyana. Box 2 shows the demographics, causes of kidney failure and outcomes. Of note, a significant number of patients were either lost to follow-up or died of unknown causes. Patients were given the option of PD or HD, and those not suitable for PD due to logistics, lack of training or medical issues (such as

previous abdominal surgery) were placed on HD via vascular access. It follows as a corollary that patients who underwent vascular access procedures were sicker with a more advanced disease process. The high cost of HD may have deterred patients from being compliant, thus leading to inadequate dialysis and early death. Despite relatively poor outcomes, we hope that with the reduction of costs associated with HD and with more teaching, results will improve over the next few years.

Tissue Typing and Cross-Matching

Tissue typing and cross-matching was done gratis at the Immunology Department of WRNMMC to ensure standard quality as required by various regulatory bodies in the U.S. Results of the tissue typing and cross-matching are displayed in Box 3. In total, 13 transplants were performed following this laboratory work. It is also interesting to note the instances where patients did not receive a transplant, or the best donor was selected from a choice of two potential donors. Patient KH for instance did not receive a kidney because of the presence of unacceptable antigens, while KS did not receive one from either of two donors because of a positive cross-match. In 2 cases, (DW and HG) tissue typing allowed us to select the better match.

Results of the First Kidney Transplant Program in Guyana

Box 4 displays the list of 13 patients that received transplanted kidneys between 2008 and 2012. Of these, 3 of the recipients died from kidney failure or other co-morbidities. The unfortunate case of the kidney failure was a result of poor compliance with the necessary anti-rejection medication, a problem all too common in the transplant population. This case

demonstrated that when offered a viable treatment option, not even the most destitute of a population will necessarily comply.[17] It highlighted the need for more patient education. All transplants were from living donors, as Guyana and most other developing countries do not have a deceased donor program. The donors were related except in one case of an unrelated altruistic donor. We are working towards establishing a deceased donor kidney program similar to United Network for Organ Sharing (UNOS).[18]

Ethical Dilemmas in Selection of Recipients and Donors

It should also be noted that our efforts in Guyana were not without ethical dilemmas. In one case, patient JG (noted in Box 3) was not transplanted despite having a living donor and a negative cross-match. Our dilemma with him was the fact that he needed a transplant, yet was suffering from bacterial endocarditis and was non-compliant with his antibiotics regimen. We questioned how well he would comply with anti-rejection medications in the post-transplant state, and we elected not to proceed; he died a few months later from septic endocarditis. In the case of recipient HG, the dilemma was that she was actually not from Guyana, but instead from neighboring Antigua. Here, the ethical question was, should a non-Guyanese native receive services provided by the Guyanese government, intended for its own citizens? After much discussion and legal counseling, and since Guyana has an open immigration policy with Antigua, we elected to proceed and she received a kidney. Other ethical issues involving potential medical tourism, commoditization of organs, and donation involving minors also came up. These cases clearly demonstrated to us that the same ethical issues that plague larger Western programs can also affect a small, nascent transplant service in a developing country.[19,20,21]

Immunosuppression

Though induction therapy is often useful in solid organ transplantation,[22] it was not employed here to avoid the associated steep cost. Also to save costs, we used generic medications: maintenance immunosuppression consisted of tacrolimus, mycophenolate and low dose prednisone (tapered off after 6 months). Random samples to check tacrolimus levels were done at our laboratories in WRNMMC. Usual prophylactic medications such as trimethorpim-sulfamethoxazole, valganciclovir, and anti-fungals were prescribed. All patients also received a ureteric stent which was removed by a local surgeon by flexible cystoscopy at 2 weeks post-op.

Skype Clinics

In conducting our renal transplant therapy in Guyana over the last 4 years, we faced a key challenge in keeping in touch with our patients as well as with the local physicians/nurses. While we found email to be sufficient for keeping in touch with the staff and indeed, some 300 emails have been communicated with them over the past 4 years, we felt that email would not be adequate for communication with the patients as most of them did not have personal computers. Instead, we elected to use Skype, the free videoconferencing software used by many for social networking. The usage of Skype in such a clinical fashion is becoming more commonplace in medicine.[23]

For a typical clinical encounter, the patients would come to the Balwant Singh Hospital in Georgetown, Guyana, where they would be set up with a computer and the staff would help connect them via Skype to the senior author at his home. With this face-to-face interaction, we would interview each patient and provide education. The physical exam was then be done during each encounter by the local Guyanese staff, who also conducted any needed laboratory tests. Our

patients conveyed to us that they enjoyed these Skype clinics; though not the same as a real physical encounter, they liked having at least some remote contact with the U.S. team, in conjunction with their local Guyanese physicians. Over 450 patients with CKD were examined during direct contact and approximately 100 patients by Skype clinics.

Teaching of Local Staff and Sustainability

We had to teach the local staff and their patients how to maintain their dialysis regimens, and how to keep proper surveillance of their immunosuppressive therapy in the post-transplant state. To begin with, the procurement of dialysis fluid and its proper usage was one challenge. For the sake of simplicity, we encouraged the usage of only one solution (Dianeal 2.5%) for dialysis exchanges. Though the full spectrum of dialysis fluids was desirable, this single selection made for better management. Both staff and patients were instructed in how to properly carry out PD and how to monitor their fluid status on a regular basis. Patients were instructed to use a blood pressure cuff, a kilogram scale, and to watch for signs of edema at home. We showed them how to keep a log and emphasized good fluid restriction practices, when necessary.

Strict adherence to immunosuppressive therapy after transplant was crucial, and we strived hard to teach both local staff and patients of this importance. It is a challenge we often face even in the Western world; and if that challenge is not met with due diligence, the invaluable donated kidney will be rejected. To this end, we encouraged patients to also keep a log of their medication use, to keep a schedule of when they needed to take them, and to keep their meds accessible at all times. We encouraged the involvement of family members to ensure patient compliance. We created a handbook for the staff detailing the work up and post-operative

management with emphasis on compliance. This educational process is crucial for the sustainability of the RRT program in Guyana.

A Public-Private Partnership

We would like to emphasize here that our efforts in Guyana came to fruition because of the intricate partnership that was established between the private and public sector. The initial idea and funding for our trip came from a philanthropic Guyanese American, who saw a dire need in his home country and sought to help. That government provided access to their hospitals and provided key materials (such as dialysis fluids) and generic medications to the patients.[24] We believe that we have demonstrated that such a model of public-private partnership can lead to the establishment of a sophisticated surgical procedure with no cost to the patient in a developing country.[25,26,27]

Initiation of a Public Health Program

We initiated a pilot program that trained local high school students from remote villages in clinical skills, such as the monitoring/recording of blood pressure, blood sugar, observing for peripheral edema, and the noting of dietary practices. In this way, they served as health advocates in their communities. The initial phase will encompass 7 villages of 1000 people each. The information will be collected and analyzed to inform the government of Guyana about the incidence and prevalence of diabetes, hypertension, kidney failure and poor sanitation. Eventually, we hope the government of Guyana will allocate resources for these diseases. We also hope that other communities in Guyana will emulate this model.[28] This volunteerism and method of surveillance is the only form of healthcare that some of these villagers have.[29,30]

The Future

We plan to continue our efforts in Guyana until the local physicians are trained in the art and science of kidney transplantation. We are currently working with the Guyana Ministry of Health to establish a deceased donor kidney program.[31] This model will be trialed in selected countries of the CARICOM conference at the end of this year which may well serve as a template for philanthropic efforts in other non-CARICOM developing countries.

To summarize, our team has created a comprehensive RRT in Guyana where none existed by a network of US-transplant heath care professionals, US-philanthropists, Guyanese health care professionals and the Government of Guyana. This work included medical, surgical, education, advocacy and a strong public health component. A number of publications in peer reviewed journals have also resulted from our work[14, 16, 21].

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Box 1: Peritoneal Dialysis patients in Guyana, South America[16]

Name	Age	Gender	Cause of kidney failure	Complication	Outcome
EG	34	F	Hypertension	None	Patient doing well with PD
JA	08	F	Acute Kidney failure	None	Died of multi-organ failure
DD	48	F	Diabetes, hypertension	Exit site abscess	I&D of abscess
GW	48	M	Hypertention, polycystic kidneys	None	Living kidney transplant from daughter
DW	25	F	Hypertension	Single episode Peritonitis	Living kidney transplant from sister
AG	49	F	Diabetes, hypertension	PD Blocked	Required temporary HD, otherwise doing well with PD
AS	51	M	Diabetes, hypertension	None	Patient doing well with PD
DB	48	F	Hypertension	None	Died of MI
FR	65	M	Diabetes	Blocked, tube replaced	patient doing well with PD
KL	44	M	Hypertension	None	Died at home, unknown reason
TS	15	M	Acute kidney failure	None	Died of liver failure
KK	43	F	Hypertension	Single episode Peritonitis	Died at home, unknown reason
GE	34	F	Diabetes	Inadequate clearance	Switched to HD
RA	76	M	Polycystic kidneys	Inadequate clearance	Switched to HD
ST	68	M	Obstructive Uropathy	None	Patient doing well with PD
PM	48	F	Diabetes	Single episode Peritonitis	Living kidney transplant from sister-in-law
KS	38	M	Hypertension	None	Living kidney transplant from brother

Box 2: Vascular Access patients in Guyana, South America (HD=hemodialysis, DM=diabetes mellitus, PCKD=polycystic kidney disease, AVF=arteriovenous fistula)

Name	Age	Gender	Cause of kidney failure	Complication	Outcome
LL	69	M	Hypertension	Superficialization	Currently on HD
BZ	36	F	DM and PCKD	None	Unknown (lost to follow-up)
AM	60	M	Hypertension	None	Died of unknown cause
BF	56	F	DM	None	Unknown (lost to follow-up)
SS	56	M	Unknown	None	Currently on HD
EB	45	F	Hypertension	Thrombosis, new AVF	Currently on HD
KH	45	F	Hypertension	None	Currently on HD
JS	45	F	PCKD	None	Died of unknown cause
UJ	60	M	Hypertension	None	Died of unknown cause
PF	34	F	DM and Hypertension	None	Died of unknown cause
DP	46	M	Hypertension	None	Unknown (lost to follow-up)
SB	43	M	Hypertension	None	Currently on HD
RK	52	M	Unknown	None	Unknown (lost to follow-up)
ON	53	M	Hypertension	None	Died of unknown cause
WG	19	F	Unknown	None	Died of unknown cause

Box 3: Tissue typing and cross-matching results between potential donors and recipients for renal transplantation. HLA mismatch=human leukocyte antigen mismatch (if it occurred, the mismatches are shown as abbreviations of the involved receptors). CDC XM is the cross-matching study done to ascertain recipient's response to donor's T- and B-cell lymphocytes. A negative response to both T- and B-cells is favorable for transplantation. A negative response following the addition of HI (heat inactivation) or DTT (dithiothreitol) is also deemed favorable; these additions demonstrate an acute (IgM-mediated) response to donor lymphocytes, that usually does not pose a barrier to transplantation. A positive CDC XM (involving either T- or B-cells) even after testing with HI/DTT served as an absolute contraindication for surgery, as did the presence of any Unacceptable Antigens (shown in the second to last column). Gray shading by recipient is for clarity.

Recipient	Potential Donor(s)	HLA Mismatch Results	CDC XM Results	Presence of Unacceptable Antigens	Transplant performed
MM	LM	1B / 1DR / 1DQ	Negative	Negative	Yes
GW	MG	1A / 1B / 1DR / 1DQ	Negative	Negative	Yes
MS	CC	1A / 2B / 2C / 1DR / 2DQ	Negative	Negative	Yes
JS	BS	1A / 1B / 1DR	Negative	Negative	Yes
GR	KR	1A / 1B / unk C / 1DR / 1DQ	Negative	Negative	Yes
AR	VR	1B / 1DR	Negative	Negative	Yes
RH	RH	1A / 1B / 2C / 1DR	Negative	Negative	Yes
MD	RB	1A / 2B / 1C / 1DR	Negative	Negative	Yes
DW	PW1	1A / 1B	Negative (HI)	Negative	Yes
	PW2	1A / 1B / 1DR / 1DQ	Negative (DTT)	Negative	No
PG	OJ	2A / 2B / 1C / 2DR / 2DQ	Negative	Negative	Yes
	SC	2A / 2B / 2C / 2DR / 2DQ	Negative	DR04	No
AB	UB	1A / 1C	Negative	Negative	Yes
KS	MS	1B / 1C	Negative	Negative	Yes
	RM	2A / 2B / 2C / 1DR / 1DQ	Negative (HI)	Negative	No
HG	JP	1A / 2B / 1C	Negative	Negative	Yes
	NG	1A / 1B / 1C / 1DR / 1DQ	Negative	Negative	No
JG	SG	1A / 1B / 1C	Negative	Negative	No
KH	DP	2A / 2B / 2C / 2DR / 2DQ	Negative	DR04 / DQ09 / DR53	No
KS	BI	2A / 2B / 2C / 2DR / 2DQ	Positive (T- and B-lymphocytes)	A01, 11 / B57 / DR07,11 / DR52	No
	DJ	1A / 1B / 1C / 2DR / 2DQ	Positive (T- and B-lymphocytes)	A24 / DR07,14 / DR52 / DQ02	No

Box 4: Transplant patients (CC = CellCept, PG= tacrolimus, PD=prednisone, DM=diabetes mellitus, HTN=hypertension, PCKD=polycystic kidney disease, oww=otherwise well, MI=myocardial infarction, CVA=cerebrovascular event)

Recipient	**Date of transplant (m/dd/yyyy)**	**Donor (initials, relation, age, gender, and post-op complications)**	**Cause of kidney failure**	**Current serum creatinine (mg/dL)**	**Current medications**	**Recipient Outcome and Complications**
MM, 18-yo male	07/12/2008	LM, mother, 43-yo female, wound infection that resolved, oww	HTN	1.0 @ last visit 1 year before death, 7.0 @ death	None	Died of kidney failure at 3 yrs post-op, as per non-compliance with anti-rejection meds
GW, 43-yo male	01/31/2009	MG, daughter, 24-yo female, oww.	DM and PCKD	2.1	CC / PG	Developed 6-cm brain lesion, cleared with reduction of immune-suppressants, oww
MS, 59-yo male	05/23/2009	CC, wife, 31-yo female, oww	HTN	1.9	CC / PG / PD	Wound infection that resolved with treatment, oww
JS, 58-yo male	05/24/2009	BS, son, 34-yo male, pain near surgical incision, oww	DM and prostatic obstruction	1.2	None	Died of MI 2 months after surgery
GR, 36-yo male	03/18/2011	KR, brother, 32-yo male, oww	Unknown	1.2	CC / PG / PD	oww
AR, 55-yo male	05/25/2011	VR, wife, 40-yo female, oww	HTN	1.3	CC / PG / PD	oww
RH, 56-yo male	05/27/2011	RH, daughter, 19-yo female, oww	HTN	1.2	CC / PG / PD	oww
MD, 38-yo male	08/31/2011	RB, brother, 43-yo male, oww	PCKD	1.0	CC / PG / PD	oww
DW, 23-yo female	12/13/2011	PW1, sister, 25-yo female, oww	HTN	1.0	CC / PG / PD	oww
PG, 48-yo male	03/08/2012	OJ, sister-in-law, 45-yo female, oww	DM and HTN	1.0	CC / PG / PD	Post-transplant DM, oww
AB, 54-yo male	03/07/2012	UB, daughter, 19-yo female, oww	HTN	1.2	None	Died of CVA 2 months after surgery
KS, 31-yo male	07/14/2012	MS, father, 60-yo male, oww	HTN	1.4	CC / PG / PD	oww
HG, 20-yo male	10/23/2012	JP, altruistic living donor, 27-yo female, oww	Unknown	1.0	CC / PG / PD	oww