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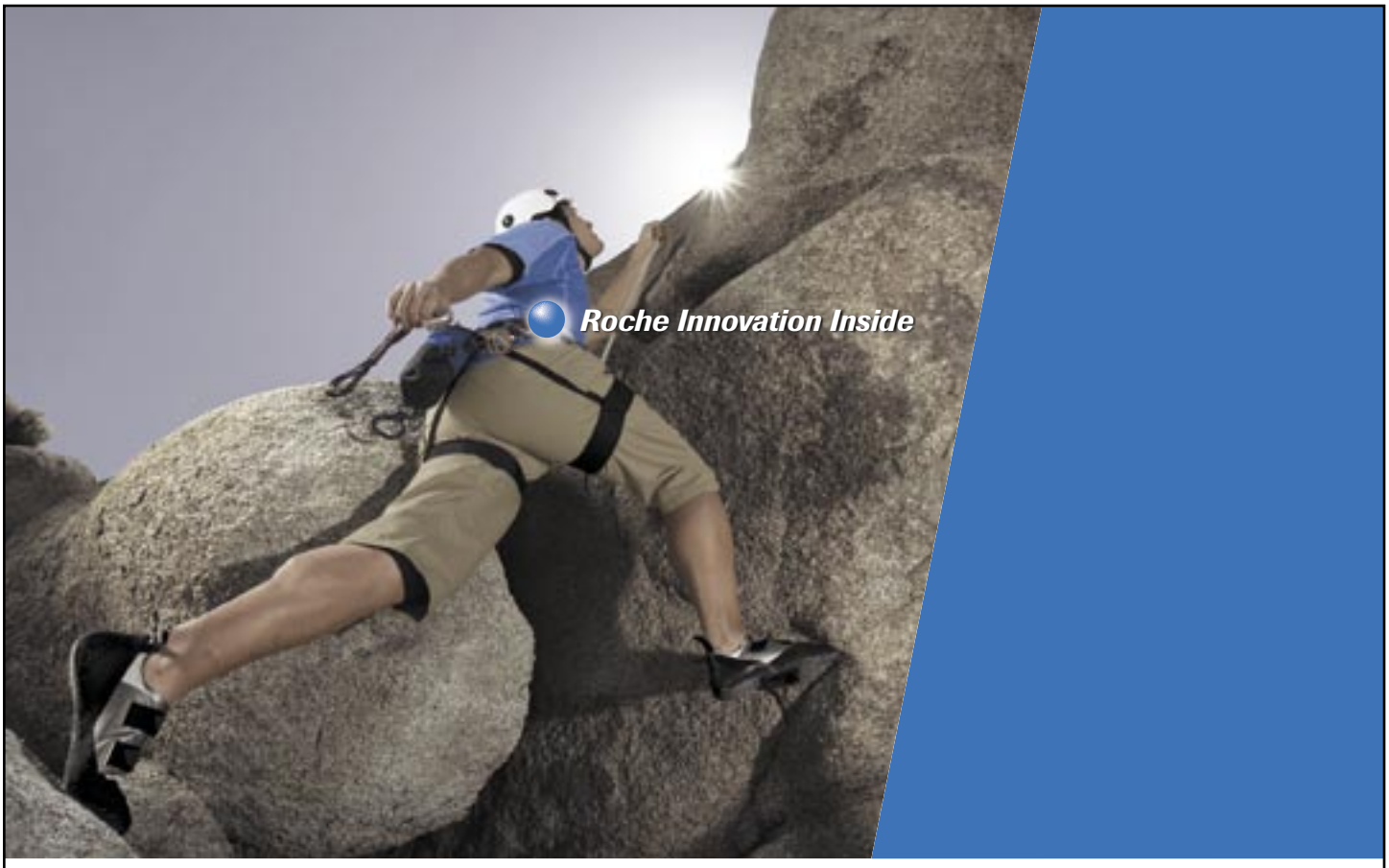
Commemorating the 40th Anniversary of Transplant in Hawai'i



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Guest Editors' Message

This year marks the 40th anniversary of organ transplantation in Hawai'i. In August 1969, St. Francis Hospital in Honolulu performed the state's first kidney transplant. Since that landmark accomplishment, the people of Hawai'i now have the latest life-saving services in transplantation, including heart, bone marrow, liver and pancreas transplants. As Dr. Livingston Wong would always say, "Transplant is a team sport," and we would not have realized his initial visions without the dedication and passion of so many individuals and organizations. This includes:

1) Our team of nurse coordinators, social workers, data coordinators, and financial coordinators assisting the physicians in evaluating potential candidates, caring for post-operative patients, and following patients for the rest of their lives.

2) Our nationally accredited laboratory staff and facilities performing: (a) HLA tissue typing capability; (b) specific immunological and drug monitoring; (c) anatomic/histologic pathology to identify and grade rejection and graft-vs-host disease.

3) The Organ Donor Center of Hawai'i, our local organ procurement organization responsible for evaluating potential deceased donors, obtaining appropriate consent from family members in a sensitive manner, and overseeing the entire process of organ donation and allocation.

4) A team of qualified surgeons and anesthesiologists to implant these organs.

5) The staff and administration of Hawai'i Medical Center East (formerly St. Francis Medical Center) including the specially trained staff of the operating room, critical care unit and transplant unit.

6) Referring physicians who have entrusted their patients with our transplant team and the transplant physicians and specialists who are involved in their care.

7) The living donors and deceased donor families who altruistically offered their loved ones' organs to others in need – during a difficult time.

We thank all of these individuals and organizations for their teamwork and tireless commitment to transplant. None of this would be remotely possible without each and everyone mentioned. We would also like to thank our sponsors, the Hawai'i Medical Association, and the editors of the HMJ for this opportunity to commemorate the 40th anniversary of organ transplantation in Hawai'i.

Linda L. Wong MD, FACS; and Alan H.S. Cheung MD, MBA, FACS

Recollections of the First Kidney Transplant in Hawai'i Forty Years Ago

Alan H.S. Cheung MD, MBA, FACS

(As interviewed with Livingston M.F. Wong MD, FACS)

Abstract

The first kidney transplant performed in Hawai'i occurred on August 10, 1969, nearly 40 years ago. This milestone achievement led to innovations in transplants of other organs and tissues that have benefited the people of Hawai'i and saved countless lives. This article is the recollections of one individual who led the first kidney transplant team to this historic event. It highlights the dramatic story behind this remarkable accomplishment, the dedication of the medical team, the leadership of the administrator of a hospital, and, most importantly, the courage of the patients who dared to risk their lives for a better tomorrow.

Visiting Professor, Dr. David Hume (left) with Dr. Arnold Siemsen and Dr. Livingston Wong (right) –1969.

Transplantation was the miracle of 20th century medicine. The first successful kidney transplant was performed at the Peter Bent Brigham Hospital in Boston between identical twins in 1954.[1] After that initial achievement, kidney transplantation soon spread across the world. But it was not for the faint of heart; it required a team that was daring and committed to innovation, and patients who were willing to risk their lives for a brighter future. The first kidney transplant was performed in Hawai'i on August 10, 1969, some 40 years ago, by a team led by Dr. Livingston Wong. This is his story.

Patients with kidney failure had very few options for long-term survival until the 1950s when Dr. Scribner developed chronic dialysis in Seattle. Even with that, these patients led a poor quality of life filled with complications. The first hemodialysis in Hawai'i was started in 1965 by a pathologist at Queen's Hospital, who learned the technique from the Cleveland Clinic. For some unclear reason, the leaders at Queen's did not feel there was a future for that treatment modality and he was told to stop. By 1967, Dr. Dudley Seto started chronic dialysis again at St. Francis Hospital, and when he left to serve in the military, Dr. Arnold Siemsen took over the fledgling dialysis program.

St. Francis Hospital at that time was led by a very innovative and, as some would say, fearless administrator, Sister Maureen Keleher, or simply Sister Maureen, as she likes to be called. She had great charisma and knew the names of practically every doctor, nurse and employee of the hospital. St. Francis had failed at being the first to perform open-heart surgery in Hawai'i earlier; Sister Maureen did not want to miss the next great medical advancement on her watch.

It was in this environment that Dr. Livingston Wong came home at the end of 1965. Dr. Wong was a local boy, graduated from Maryknoll High School and majored in chemistry at the University of Hawai'i. After toying with the idea of becoming a scientist, he finally decided to become a doctor and enrolled at the Oregon Health and Sciences University in Portland where he graduated near the top of his class. After deciding to pursue a career in surgery, he was encouraged by Dr. J. Engelbert Dunphy, the Chairman of the Department of Surgery, to seek residency training at the Mecca of surgery in Boston. That meant the Massachusetts General Hospital, a prominent teaching hospital of Harvard Medical School. To say that it was difficult to get accepted to the "Mass General" would be a gross understatement, particularly as a minority in the 1960's. Dr. Wong was only the third Asian-American to graduate from the prestigious surgery residency program. While in Boston, he met and learned alongside many of the future leaders of American surgery.

But by the end of 1965 Dr. Wong felt homesick. Along with his growing family, he moved back to Hawai'i where he entered into private practice in general surgery. He spoke of the trials and tribulations of starting a practice in those early days, despite his superior training. But after two years, his practice flourished, and being young and curious, he quickly became involved with the dialysis program at St. Francis Hospital. There he performed the Scribner shunts and various vascular access procedures that were the lifelines for these dialysis patients.

In February 1968, Dr. Herbert Chinn, a prominent local urologist, approached Dr. Siemsen and Dr. Wong about starting kidney transplants in Hawai'i. Dr. Wong told Dr. Chinn, "Give me a chance to look into it." Dr. Wong called his friend and mentor, Dr. Paul Russell at the Massachusetts General Hospital (MGH) for advice. Dr. Russell had helped start the kidney transplant program at the MGH in 1965 and felt it was doable. But before Dr. Wong pursued it further, he wanted to get the support from a local hospital. He spoke with the CEO of Queen's Hospital in March 1968 and got a lukewarm response. But Sister Maureen at St. Francis Hospital was excited about the idea and encouraged him to investigate further.

As fate would have it, the Second International Congress of the Transplantation Society took place in New York City in June 1968. Dr. Wong thought it would be a great opportunity to learn about this new field and meet some of the pioneers in transplantation. A trip to New York was very expensive in those days, and while he could hardly afford it, he paid for his own way and roomed with a friend there.

While at the meeting in New York, Dr. Wong met up with his mentor, Dr. Paul Russell who introduced him to the charismatic transplant surgeon, Dr. David M. Hume, who at that time was the Chairman of the Department of Surgery at the Medical College of Virginia. Dr. Hume was going to be giving a lecture at the Sheraton Hotel in Waikiki the following summer and he would be able to help Dr. Wong with the first kidney transplants at that time. Dr. Hume had served as a US Navy surgeon at Pearl Harbor from 1945 to 1946 where he was stationed at Tripler in Aiea. Two of his children were born at Kapiolani Hospital and he had fond memories of Hawai'i, so coming to Hawai'i would be no great sacrifice.

As it turned out, Dr. Hume was the perfect collaborator. He was an excellent teacher, and has been described as having an "unbound, youthful enthusiasm that was infectious and readily transmitted to people around him."[2] He had been a chief resident surgeon at the Peter Bent Brigham Hospital and director of the Laboratory for Surgical Research at Harvard Medical School where he had perfected the surgical technique of kidney transplants in dogs. Were it not for his Navy service again from 1953 to 1955 from 1953 to 1955, he might well have performed the historic world's first kidney transplant in Boston.

After the New York meeting, Dr. Wong visited the transplant program at the Medical College of Virginia for three days. In 1968, they were doing about 20 to 30 kidney transplants a year. While he did not actually see a transplant during this visit, Dr. Wong did obtain their clinical immnosuppression protocols and got a good feel for what a transplant program should look like.

Before coming home, Dr. Wong had one more stop to make in Los Angeles. Besides the surgery and the post-operative immunosuppression, another crucial component to a successful kidney transplant was the tissue typing and cross-match. Dr. Paul I. Terasaki was the head of the Tissue Typing Laboratory at UCLA and a pioneer in HLA definition, cross match, histocompatiblity, analysis of transplant factors, and simple cold storage and kidney sharing. He was a very generous person and Dr. Wong spent three days learning all about clinical transplantation and tissue typing from him. At the end of the visit, the two decided that Dr. Wong would send Dr. Terasaki the blood specimens of the patients and donors, and he would do the tissue typing and cross-matching before the kidney transplants.

Back home in Hawai'i, the winter of 1968 and spring of 1969 were busy times for Dr. Wong. He wanted to develop a team of surgeons, anesthesiologists and nurses who would be proficient in performing the first kidney transplants in the operating room. By that time, he had received the full support of Sister Maureen to proceed. So he built a dog lab at the St. Francis Hospital to practice. He and some friends would go to the pound and get dogs that were over 25 lbs. These dogs were housed in cages in the old obstetrics section of the hospital. In all, four or five pairs of dogs were used for the donor and recipient kidney transplant operations. His team of surgeons included Dr. Glenn Kokame, a general surgeon, Dr. Walton Shim, a pediatric surgeon, Dr. Richard Pang, a general and thoracic surgeon, and Dr. Herbert Chinn, the urologist who would be doing the living donor operations.

By early 1969 there were about 15 to 20 patients on chronic dialysis in Hawai'i. Dr. Wong and the nephrologists approached the younger patients who had potential living-related donors and offered them the opportunity for a kidney transplant. Each patient was carefully selected and diabetic patients were excluded at that time because of the higher risk. Five patients were selected, but only three were interested and had willing donors. Their blood sample was sent to Dr. Paul Terasaki's lab for tissue typing and cross matching. By the summer of 1969, the patients were chosen and Dr. David Hume was kept appraised of the selections. Everything was ready.

Dr. David Hume flew in from the Mainland on Friday, August 8, 1969. Dr. Wong picked him up at the airport and drove him to his hotel in Waikiki. The next day Dr. Wong rushed to Kapiolani Hospital where his 5th and youngest child, Lyle, was born. It was a hectic day. The first pair of donor and recipient patients was admitted to St. Francis Hospital on Saturday, August 9. The transplant was deliberately scheduled on a Sunday – the hospital would be quiet and there would be fewer distractions from the media. The public did not know what was going on at that hospital on Liliha Street, but the *Honolulu Star-Bulletin* on August 8, 1969 noted in *Dave Donnelly's Hawai'i* column, "Medical history is going to be made here over the weekend. We can't divulge any details except it will be a first insofar as Honolulu hospital operations are concerned. The doctors involved are understandably concerned about it and want to avoid any advance publicity splash."[3]

There were two operating rooms available on that Sunday, August 10, 1969. The historic first kidney transplant was between two Kailua brothers. James C., the recipient, was 42 years old with membranous glomerulonephritis. He and his wife operated the old Skylane Inn Bar on Waiwai Place. He had been on chronic hemodialysis for 17 months. His brother, Thomas C., age 44, was the donor. The donor was wheeled into the operating room, put under general anesthesia by Dr. Clifford Chock, and underwent a standard left donor nephrectomy. The surgeons at the table were Dr. Herbert Chinn, Dr. Glenn Kokame, and Dr. Livingston Wong. The left kidney was carefully removed, flushed with cold Ringer's lactate and stored on ice. The donor procedure lasted about six hours.

Then the recipient was put to sleep, again by Dr. Clifford Chock. Dr. Livingston Wong, Dr. David Hume, and Dr. Richard Pang were at his side. A curved incision was made in the right iliac fossa and the right iliac artery and vein were dissected carefully. The donor kidney was then taken out of the ice bath. The donor renal artery was sutured to the patient's right hypogastric artery, end-to-end, with great care to avoid stenosis. The donor renal vein was then sutured end-to-side to the patient's right external iliac vein. The vascular clamps were removed and the kidney pinked up nicely. Finally, a ureteroneocystostomy was done as described by Ledbetter and Politano, thereby connecting the ureter to the bladder.

After completion of the ureteral anastomosis, however, the transplanted kidney turned dusky, a hallmark of the dreaded hyperacute rejection. Dr. Hume had seen it before. He recommended a biopsy be done immediately; the results confirmed neutrophilic infiltration already occurring within the transplanted kidney. There was nothing else to do but wait. The recipient operation lasted five hours; altogether after nearly 11 hours of surgery, the team felt exhausted.

James was then taken to the Recovery Room -- there were no intensive care units in those days – with one to one nursing. The immunosuppression used was azathioprine and prednisone; no antilymphocyte antibodies were used. The kidney functioned the first night. It continued to make urine for a few more days, then stopped. By day 5 after the transplant, the patient was showing signs of rejec-

tion. The doctors decided to take the patient back to surgery for an open biopsy of the transplanted kidney on day 9. There they found a lifeless kidney and a transplant nephrectomy was done. Repeat cross-match at Dr. Terasaki's lab later confirmed a positive cross reaction between the donor and the recipient, suggesting preformed antibodies present that ultimately led to the hyperacute rejection. The team felt bad, but as Dr. Wong later said, "You gotta live with it."

That was the sentiment of the patient and the donor, too. Thomas, the donor, was interviewed by the *Honolulu Star-Bulletin* after his discharge from the hospital and said they were disappointed that the graft didn't take.[4] "That's one of the breaks of the game," he said. "The doctors – and I really can't say enough for them – were very honest with us from the very beginning. We knew it wasn't a sure thing. Boy, you sure couldn't ask for a better bunch of doctors. All of those guys are just fantastic. The surgeons, the mainland consultant (Dr. David M. Hume) – all of the team. Just tremendous, " he continued. "I don't think quite a few of them got any sleep many of those nights. It seemed they were always there, especially the chief surgeon (Dr. Livingston Wong) and Dr. Arnold W. Siemsen (director of the hospital's hemodialysis program)," he said.

Dr. David Hume had initially planned on staying at the Hilton in Waikiki for one week, but eventually ended up staying for one month. He loved Hawai'i and the nightlife of Waikiki. He and Dr. Wong made rounds together on the patients about two to three times a week, but would converse nightly. During the day, Dr. Hume would go out surfing.

Two additional transplants were done while Dr. Hume was in Hawai'i. The second transplant occurred on Wednesday, August 13, 1969. The patient, Robert O. was a 24-year-old local Japanese-American man, a University of Hawai'i student with chronic glomerulonephritis who had been on hemodialysis for two years. He was young, single, and wanted to get off dialysis. His brother, one year younger, was a willing donor. After reperfusion of the transplanted kidney, it pinked up nicely and continued to function without any problems. The patient remained in the hospital for two weeks. He did well after discharge, later got married, and ultimately retired many years later and moved to Michigan where he died in 2001.

The third kidney transplant in that series occurred on Sunday, August 17, 1969. That transplant kidney also worked well.

The first kidney transplant in Hawai'i was just one of many more firsts in the remarkable career of Dr. Livingston Wong. The first cadaveric kidney transplant took place on February 8, 1971 after he and Dr. Young Paik started Hawai'i's Tissue Typing Lab at the end of 1970. Dr. Wong then started the "911" emergency ambulance service for the state from 1972 to 1979, mainly to ensure appropriate care of trauma victims, but also partly to make organ donation feasible in Hawai'i. Then he led another team to perform the first bone marrow transplant in Hawai'i in 1978, partly as a means to fully utilize the Tissue Typing Lab locally. He then encouraged and recruited other young transplant surgeons to Hawai'i, which led to heart transplants in 1984, liver transplants in 1993, and pancreas transplants in 1993.

This has been an incredible journey. The people of Hawai'i can be grateful to the daring and innovation of the medical team, the courage of the administrators at St. Francis Hospital, and the faith of the patients who helped make history 40 years ago. Since that historic day in 1969, nearly 1,100 kidney transplants have been performed at St. Francis Medical Center/ Hawai'i Medical Center East. We hope the innovations and stories will continue.

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Forty Years of Kidney Transplantation in Hawai'i

Alan H.S. Cheung MD, MBA, FACS; Linda L. Wong MD, FACS; Fong-Liang Fan MD, FACS; Whitney M.L. Limm MD, FACS; Hiroji Noguchi MD, FACS; Makoto Ogihara MD; and Livingston M.F. Wong MD, FACS

Abstract

The first kidney transplant in Hawai'i was performed in August 1969. In the following 40 years, nearly 1,100 kidney transplants have been performed locally. The most common etiology leading to transplantation was chronic glomerulonephritis. Patient and graft survivals after a kidney transplant have progressively improved, particularly after the introduction of cyclosporine in 1984. More living donor transplants are being performed over the past decade due to the shortage of suitable deceased donors. The overall one-year patient and graft survival rates now are 97% and 97%, respectively; these results exceed the national averages.

Introduction

The first kidney transplant in Hawai'i was performed in August 1969 in a 42-year-old man with membranous glomerulonephritis, which is detailed in this issue of the *Hawai'i Medical Journal*. He had been on chronic hemodialysis for 17 months prior to the transplant. Since that initial accomplishment, the care and quality of life for many patients with end-stage renal disease (ESRD) have improved tremendously. The growth and development of kidney transplantation locally was crucial to our island state where our geographic isolation might otherwise force many patients to travel to the mainland for kidney transplants or to remain on dialysis indefinitely without surgery.

The results of our initial 25 years of kidney transplantation in Hawai'i were published in the *Hawai'i Medical Journal* in March 1994.[1] The aims of this current study were to examine the kidney transplant results and trends in Hawai'i over the past 40 years, particularly over the past 20 years, and to compare these results with available national statistics.

Methods

Between August 1969 and December 2008, a total of 1,092 kidney transplants were performed at St. Francis Medical Center/ Hawai'i Medical Center East in Honolulu. The approach to patient care, including recipient and donor selection, timing of the transplant, surgical techniques, immunosuppressive protocols, treatment of acute rejection, and ancillary care have been similar to those described in detail in the literature.[2,3,4] Particular attention was paid to the 802 kidney transplants performed over the past 20 years, from 1988 to 2008 where data was available for analysis using the UCLA/United Network of Organ Sharing (UNOS) Scientific Registry.

The UNOS Scientific Registry was created in October 1987 following enactment of legislation contained in the Transplant Act of 1984 with records of all kidney transplants performed in the United States. Prior to 1987, kidney transplantation registry data was maintained by Dr. Paul Terasaki at the UCLA Tissue Typing Laboratory. This retrospective review used the UNOS Kidney Transplant Registry database and locally available charts at St. Francis Medical Center/Hawai'i Medical Center East.

As mentioned in our previous analysis in 1994,[1] the powerful drug, cyclosporine A (CsA) was introduced commercially after 1984 and was used on all kidney transplants to prevent graft rejection, in addition to steroids and azathioprine. OKT3 and anti-lymphocyte globulins also were available to treat acute rejections. Then around 1995, mycophenolate mofetil (MMF) replaced azathioprine as the new purine synthesis inhibitor, and the new calcineurin inhibitor, tacrolimus was also available as a potential replacement for CsA. In early 2000, another new class of monoclonal antibiodies became available, such as daclizumab that can block interleukin-2 (IL-2) receptors as induction therapy to prevent acute rejection.

This current analysis looked at our results over the past two decades in the CsA and tacrolimus era. Patient and graft survival rates were obtained using actual clinical results. Graft loss was defined as the earliest return to maintenance dialysis, retransplantation, or death. All causes of death were included in the analysis.

Results

The number of kidney transplants performed each year since the first transplant in 1969 and the source of donor kidneys are shown (Fig 1). A total of 1,092 kidney transplants were performed over the past 40 years. Only living-related donor (LRD) kidney transplants were done in 1969 and 1970. Since that time, most of the donor organs have come from deceased donors (DD), with a total of 814 deceased vs. 278 living donor (LD) kidneys. A comparison of DD and LD kidney transplants by decade over the past 40 years is shown (Fig 2). The total number of kidney transplants has increased steadily over each decade. While DD were the major source of kidneys in each decade, the percentage of LD has gradually increased from 21% in 1989-1998, to nearly 30% in 1999-2008. The relatively stable number of DDs compared to the ever-expanding demand for kidney transplants necessitated the use of greater number of LDs.

In the early years prior to 1994, only LRDs were used. These were genetically related individuals such as siblings or parents who were willing to donate and had a greater chance of a better Human Leukocyte Antigen (HLA) match. As the need for kidneys increased, more creative inclusion of LDs were applied. Figure 3 shows the type of LDs used from 1994-2008. Living Non-Related or Un-Related Donors (LUD) were first used in 1994 between marital spouses who were obviously not genetically related. This allowed for the availability of a kidney for transplant, but at a sacrifice of a potentially poorer HLA match. Then in 2002, altruistic LDs were used. These were LDs in the community who, out of compassion and altruistic intentions, offered to donate one of their kidneys to anyone who might benefit from a kidney transplant. These donors have no prior relations with the recipients. In 2005, trading of living kidney donors was also initiated to address the issue of incompatible blood types between recipients and potential donors. For example, if a recipient with blood type A had a potential LD who had blood type

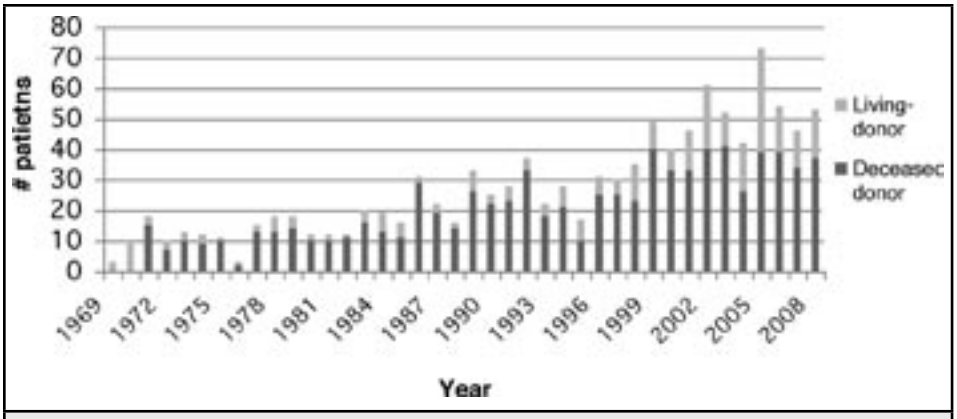

Figure 1.— Kidney transplants performed in Hawai'i 1969-2008

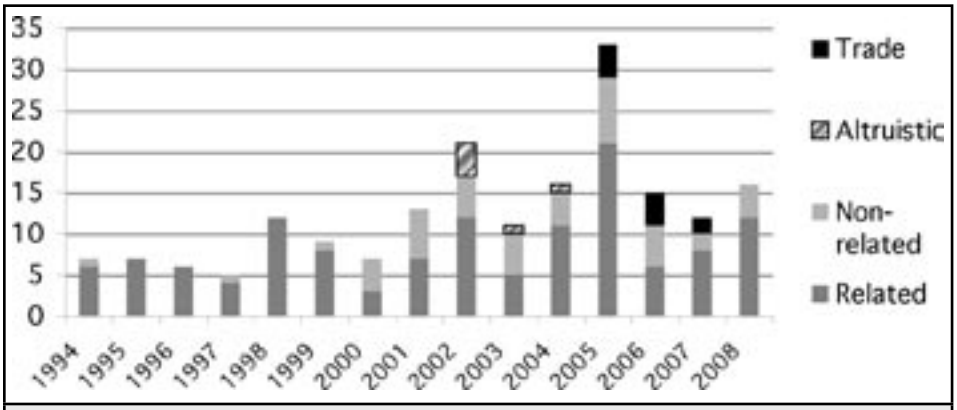

Figure 2.– Types of living donors 1994-2008 (prior to 1994, all living donors were related donors)

Table 1.— Patient Demographics (1988- 2008)

	Patients (%) (n=802)
Race	
Asian	419 (52.2%)
Pacific Islander	198 (24.7%)
White	97 (12.1%)
Multiracial	79 (9.9%)
Black	9 (1.1%)
Hispanic	9 (1.1%)
ABO blood type	
O	341 (42.5%)
A	289(36.0%)
B	120 (15.0%)
AB	52 (6.5%)
Age Range	
1-5 years	7 (0.9%)
6-10 years	6 (0.7%)
11-17 years	26 (3.2%)
18-34 years	183 (22.8%)
35-49 years	245 (30.5%)
50-64 years	264 (32.9%)
65+ years	71 (8.9%)

B, kidney transplantation cannot take place due to blood type incompatibility. However, if they could find a recipient-donor pair in the similar situation, but in the reversed order with the recipient having blood type B and the potential donor having blood type A, then they could trade donors with each other, thereby benefiting both parties.

The demographic data of the kidney transplant patients over the past 20 years are listed in Table 1.[5] Asians made up the majority of our kidney transplant ethnic groups, followed by Pacific Islanders and Caucasians. The most common ABO blood group was O, followed closely by A. Kidney transplants were most commonly performed in the 50-64 year-old age group, followed by 35-49, then 18-34 year-old age group. Some of the common causes of renal failure for our population are listed (Table 2), with chronic glomerulonephritis being the most common.

Over the past 20 years, both the patient and kidney graft survival rates were better for adult patients with LDs as compared to DDs (Fig 4 – 7). The current one-year patient survival with a LD is 99.2% vs. 96% with a DD. The current one-year kidney graft survival with a LD is 98.4% vs. 94% with a DD. The results of the last decade were better then the previous decade in all measures of patient and graft survival rates at one, three, and five years.

The UNOS Scientific Renal Transplant Registry also provided data based on 38,693 renal transplants performed at all US transplant centers between 07/01/2005 and 12/31/2007 for 1 Year Cohorts, and between 01/01/2003 and 06/30/2005 for 3 Year Cohorts.[6] These national statistics were compared to Hawai'i's in Table 3: The national overall one-year patient and kidney graft survival rates for DD kidney transplants were 96.4% and 92.8%, respectively; compared to our results of 96.7% and 97.0%, respectively. Our results also compared very favorably with those of larger transplants centers in Northern California.

Table 4 shows the distribution of the kidney donor types over the past two decades. Overall, 72.8% of our organs were from DDs and 27.2% from LDs over the past 20 years. But on a percentage basis, LDs accounted for 31% of all donors in the last 10 years vs. 19.3% the prior decade; many of these were attributed to the increase in LUDs over the past decade. Even in the DD category, less

Table 2.— Etiology of End-stage Renal Disease	
Primary Diagnosis	Patients (%) (n=802)
Chronic Glomerulonephritis	296 (36.9%)
Diabetes Mellitus	182 (22.7%)
Hypertensive nephrosclerosis	118 (14.7%)
Lupus nephritis	46 (5.7%)
Polycystic kidney disease	43 (5.4%)
Retransplant	19 (2.4%)
Pyelonephritis/Obstructive Nephropathy	13 (1.6%)
Other	85 (10.6%)

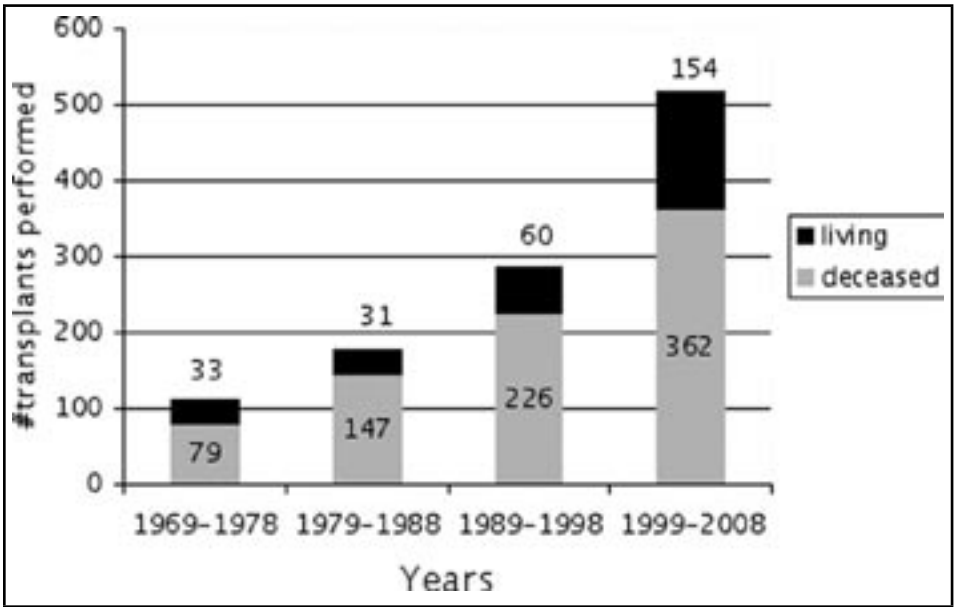

Figure 3.— Comparison of deceased and living-donor kidney transplants by decade over 40 years

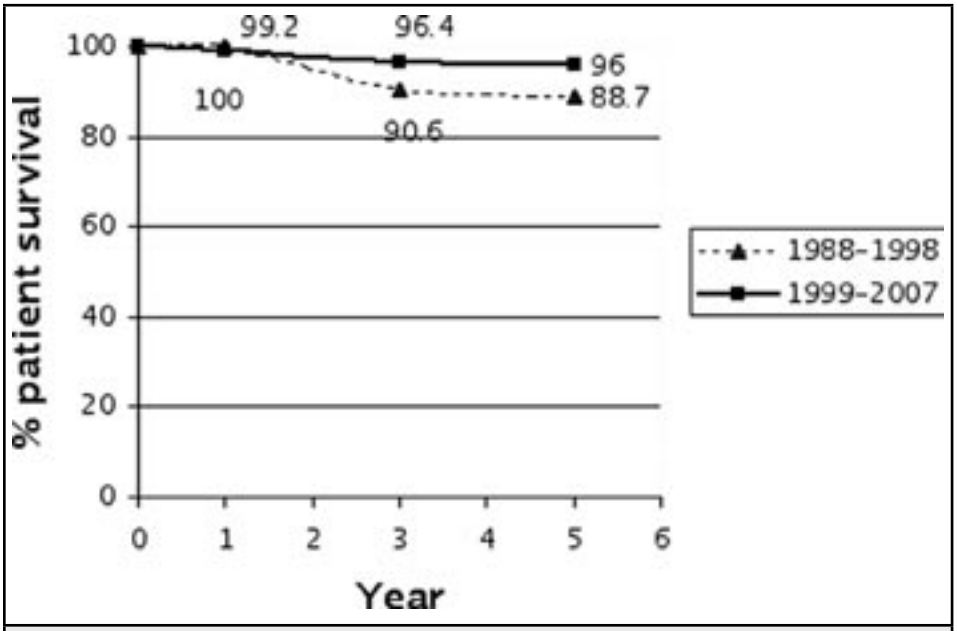

Figure 4.— Adult patient survival, living-donor kidney transplants

were due to standard criteria donors (SCD) who are < 50 years of age. There has been a tremendous increase in the use of expanded criteria donors (ECD) over the past decade; these are donors > 60 years of age or > 50 years old with hypertension, creatinine level >1.5 mg/dl, or death from stroke. We have also used donors after cardiac death (DCD) increasingly over the past decade as the shortage of donors became more severe.

Discussion

Since the first kidney transplant was performed in Hawai'i 40 years ago, kidney transplantation has become the treatment of choice for selected patients with ESRD. As the sole transplant center for Hawai'i and the Pacific basin, Hawai'i Medical Center East continues to address the needs these patients. In this retrospective review, the lessons learned over the past 40 years have been tremendous. This retrospective analysis reviews our past accomplishments, compares our latest results with those of other centers in the United States, and offers a glimpse of the future of kidney transplantation for patients in Hawai'i.

Since 1969, nearly 1,100 kidney transplants have been performed in Hawai'i. Nearly half (516) of these were performed over the past decade. Initially, only LRD kidney transplants were performed, both for the superior outcome because of better HLA match and also for the availability of these organs. The problem, however, was that not all patients had available LDs and nephrectomy does pose risks to the LD. Therefore, starting in 1972, DDs became the predominant source of kidneys. But over the past two decades, the demand for kidney transplants continued to exceed the supply of even these DD sources. Over the past decade, the percent of LDs again climbed relative to the total number of kidney transplants performed.

Interestingly, the characteristics of both the LDs and DDs also evolved over the past two decades. Initially only LRDs were used; these were genetically related individuals such as siblings or parents who conferred a superior HLA match. However, starting in 1994, LUDs were used. These were typically marital spouses who were willing donors, but gradually evolved to include friends and even strangers not known to the recipient, as in altruistic donors. Then to be even more creative, trades among unsuitable donor-recipient pairs were also performed.

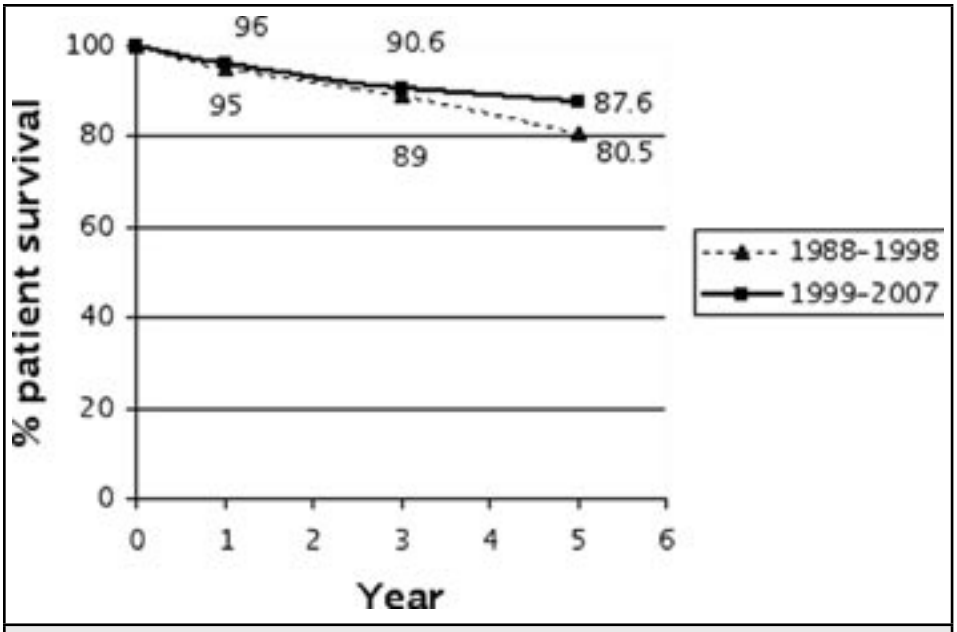

Figure 5.— Adult patient survival, deceased-donor kidney transplant

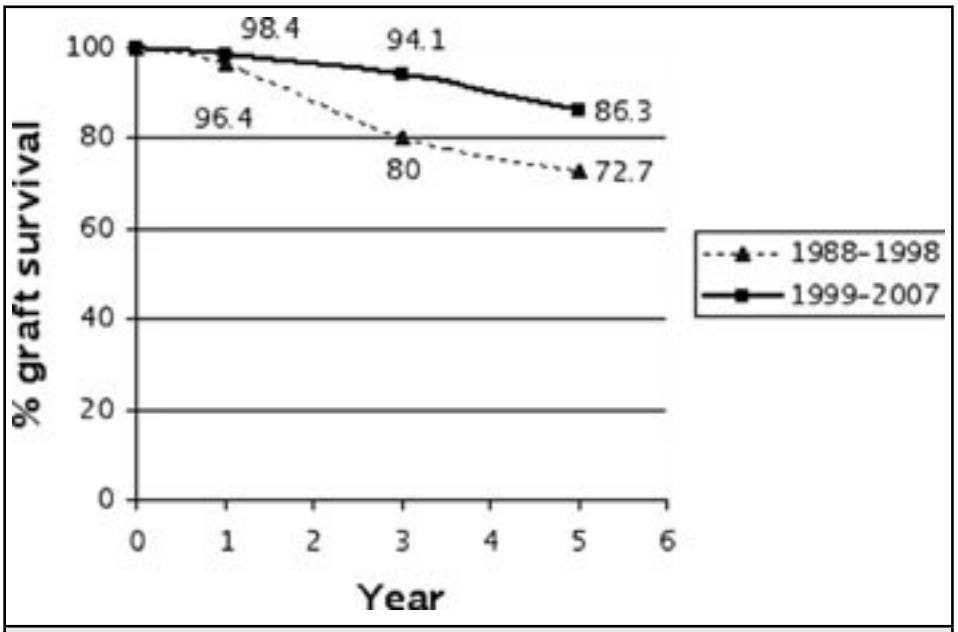

Figure 6.— Adult graft survival, living-donor kidney transplants

Table 3.— Overall Patient and Graft Survival 2003-2007

	Hawai'i	CPMC*	UCSF**	US total
1 yr graft survival (# patients)	97.01% (n=134)	95.54% (n=411)	95.31% (n=693)	92.8% (n=38,693)
3 yr graft survival (# patients)	87.5% (n=112)	88.05% (n=385)	86.71% (n=745)	83.26% (n=36,571)
1 yr patient survival (# patients)	96.71% (n=128)	95.74% (n=241)	96.86% (n=612)	96.41% (n=34,029)
3 yr patient survival (# patients)	91.96% (n=112)	88.89% (n=225)	92.64% (n=666)	90.98% (n=32,064)

*CPMC =California Pacific Medical Center, San Francisco
**UCSF = University of California, San Francisco

As for DDs, in the earlier decades only ideal standard criteria donors (SCD) were used. These were typically young, otherwise healthy donors dying from brain death caused by trauma. But as the demand for organs climbed, less stringent criteria for deceased organ donations came into being – the expanded criteria donor (ECD) who were older and with less desirable health history such as hypertension, stroke and even diabetes. Then in the latest decade, non-brain dead donors were used – the donors after cardiac death (DCD). These donors typically had severe, irreversible brain injuries that did not fulfill the clinical criteria for brain death, but their families wanted to withdraw life-support. In selected cases, these patients can be used as donors after the heart stopped and they have been pronounced dead by their treating team. Only after a period of time from pronouncement of cardiac death by non-transplant physicians, can the transplant team then procure the organs. The first such DCD donor was described in this *Journal* in 2000.[7]

As the demand for kidneys continues in the future, the need for these types of non-standard LDs and DDs will continue. Efforts by the Organ Donor Center of Hawai'i to educate the public and healthcare organizations have been tremendous. The Transplant Institute at the Hawai'i Medical Center East continues to encourage living donation for all potential transplant candidates.

The kidney transplant patient demographics have not changed much from our previous analysis of 1994.[1] Asians continued to be our largest ethnic group, but Pacific Islanders have replaced whites as the second largest group. The top two ABO blood types continued to be O and A. The cause of renal failure leading to transplantation continued to be led by chronic glomerulonephritis; however, diabetes mellitus nearly doubled as the second leading cause, increasing from 9.3% to 22.7% over the past two decades. As the Baby Boomers age, the future kidney transplant recipients will likely be older with chronic diseases such as diabetes and hypertension as the cause of renal failure.

Over the past 20 years, Hawai'i's program continued to see improvements in adult patient and graft survival rates for both LD and DD kidney transplants for one, three and five years. As the overall patient and graft survival rates have improved over the years, a milestone improvement seems

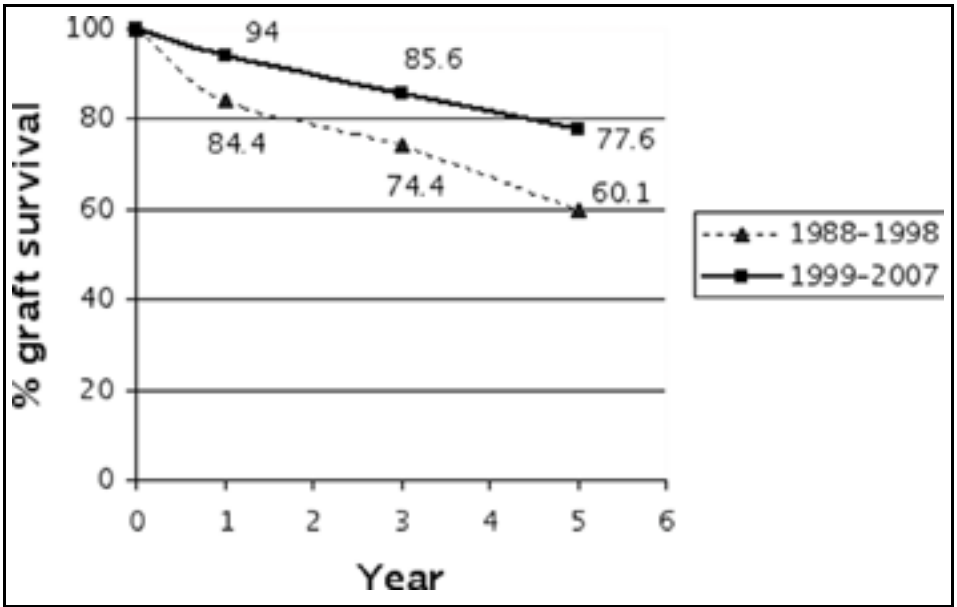

Figure 7.— Adult graft survival, deceased-donor kidney transplants

Table 4.— Number of Kidney Transplants in Hawai'i from 1988-2008, UNOS Data

Donor Type	1988-1997	1998-2008	Total
Deceased:			
DCD	2 (1%)	16 (4.4%)	18 (3.1%)
ECD	9 (4.3%)	102 (27.8%)	111 (19.3%)
SCD	198 (94.7%)	249 (67.8%)	447 (77.6%)
Total (% of TOTAL)	209 (80.7%)	367 (69.0%)	576 (72.8%)
Living:			
Related	46 (92%)	103 (62.4%)	149 (69.3%)
Unrelated	2 (4%)	62 (37.6%)	64 (29.8%)
Not Reported	2 (4%)	0 (0%)	2 (0.9%)
Total (% of TOTAL)	50 (19.3%)	165 (31.0%)	215 (27.2%)
TOTAL NO. TRANSPLANTS	259	532	791

Based on OPTN Data as of March 6, 2009. DCD = Donation after Cardiac Death. ECD = Expanded Criteria Donor. SCD = Standard Criteria Donor.

to be that of better immunosuppression. As we have shown previously, the survival data improved dramatically after 1984 with the introduction of CsA.[1] This new immunosuppressive regimen presumably allowed for a lower incidence of graft loss from rejection. Other new drugs also became available in the 1990s and early 2000, such as tacrolimus, MMF, OKT3, thymoglobulin, daclizumab, and rapamycin all have contributed to lower rejections. Although it is not clear in the data, probably other factors contributed to better outcomes including the increased experience of the transplant team, improved ancillary support, better intensive care management, and newer antibiotics such as ganciclovir for treatment of severe cytomegalovirus infections. In the future, better immunosuppressive medications will be available and the challenge will be to choose among the multitude of drugs that offer the best benefit with the lowest toxicity.[8]

The LD kidney transplants continued to be much better than the DD transplants in long-term graft survival. This was true in all other reports because a LD allows for better HLA matching and shorter ischemic times, thereby avoiding preservation injury from acute tubular necrosis (ATN).[2]

Our current one-year patient survival was 97% and one-year graft survival was also 97%, both improved from our prior analysis. Retrospective reviews and comparison reports are important both to show where we have been and where we could be headed in the future. Data from UNOS compiling national statistics and large center reports have been most helpful.[6,9] As the data indicate, our one-year patient and graft survival rates both exceed the national averages. As compared to larger transplant programs in Northern California, our results clearly speak for themselves. This fact should be very reassuring to the people of Hawai'i who relied on St. Francis Medical Center/ Hawai'i Medical Center East exclusively for their transplantation needs.

Conclusions

Over the past 40 years, both dialysis and renal transplantation have advanced to the point where patients with ESRD can be managed with good long-term success rates. Data have indicated that patient survival after transplantation is far superior to that of dialysis in selected patients with ESRD. In addition, kidney transplantation continues to be a more cost-effective treatment than dialysis long-term. Perhaps more importantly, the quality of life after successful transplantation is markedly better than dialysis. The transplant program locally continues to thrive with patient and graft survival rates that are comparable to national averages. Thus, in 2009, all patients with ESRD should be considered for referral as transplant candidates.

Acknowledgements

As with any large clinical endeavor, numerous individuals from all specialties must work together to make the vision possible. We owe special thanks to all the nephrologists in Hawai'i for their excellent care of patients with ESRD. The staff of the Organ Donor Center of Hawai'i has been instrumental in increasing the number of deceased donors in Hawai'i. And finally, the staff of St. Francis Medical Center, now known as the Hawai'i Medical Center East, has been instrumental to the excellent outcomes of these patients.

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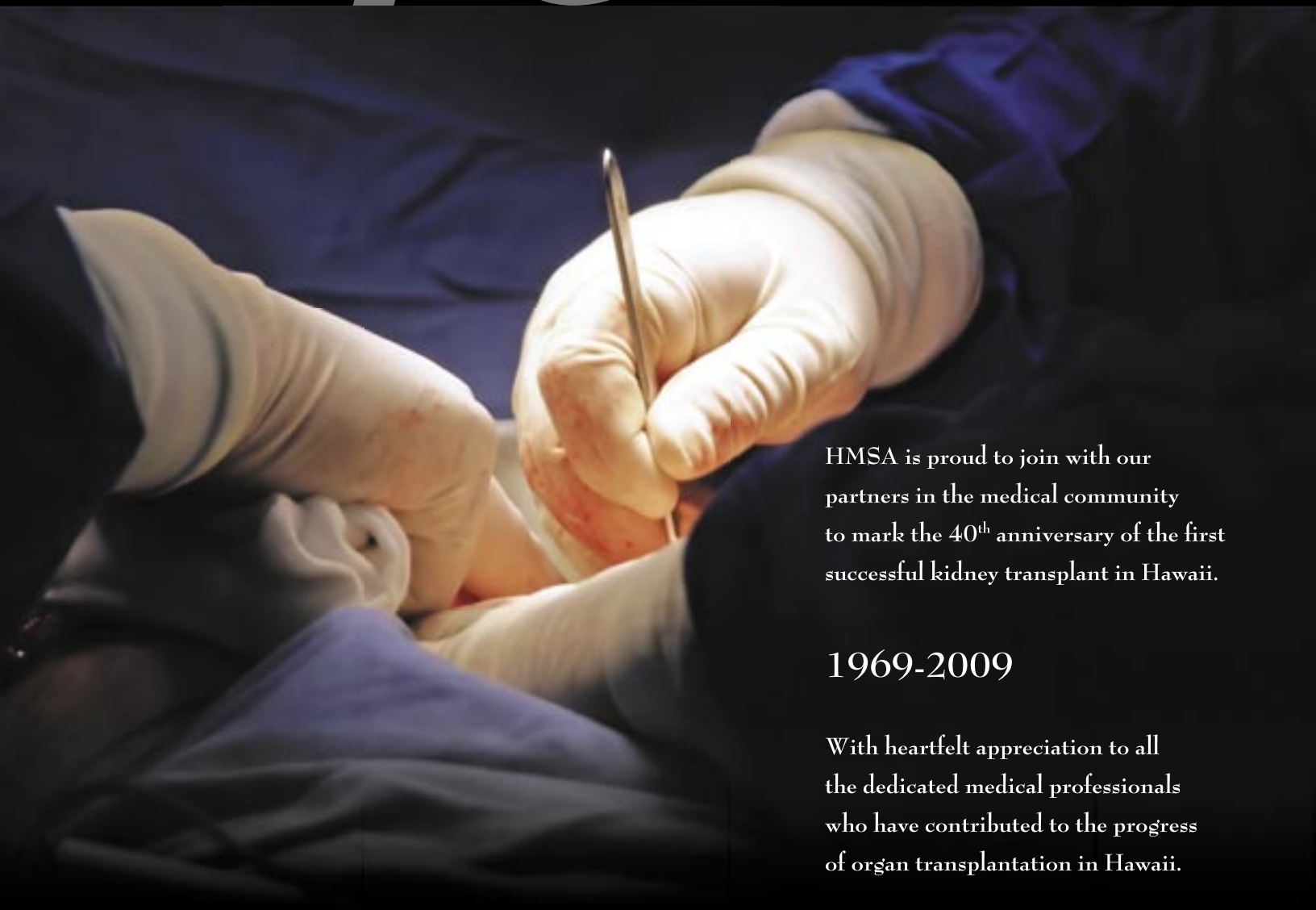
Commemorating 40 Years of Second Chances



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Incidence of BK Polyomavirus After Kidney Transplant in Hawai'i: A Preliminary Report

Makoto Ogihara MD; Linda L Wong MD; Whitney ML Limm, MD; and Alan H.S. Cheung MD, MBA

Abstract

BK polyomavirus (BKV) has recently gained interest as an important opportunistic infection after kidney transplantation. Reactivation of BKV is common in kidney transplant recipients with a prevalence of 45-50%, although BKV nephropathy (BKVN) only affects 1-5% of transplant patients. Diagnosis of BKV is challenging due to lack of specific signs and symptoms. Once BKVN develops, graft loss is common. The most widely accepted risk factor is intense immunosuppression, and reduction of immunosuppression is the principal treatment. Since early diagnosis is key to successful treatment of BKVN, some transplant centers have started screening urine and plasma for BKV load in kidney transplant patients. At Hawai'i Medical Center East, we began prospective monitoring of urine and plasma BKV load in August 2008. From August 2008 to May 2009, a total of 28 patients underwent kidney transplant. Among 26 studied patients, three developed BKV infection (incidence of 12%). All three patients responded to reduction of immunosuppression and their allograft kidney functions remained stable.

Introduction

BKV infection is common in childhood and is largely asymptomatic. Between 60% to 80% of immunocompetent adults have serological evidence of previous exposure,[1] but the virus remains latent. BKV can reactivate due to immunologic changes related to age, pregnancy, diabetes mellitus, immunosuppression or treatment of rejection.[2] Kidney transplantation is the treatment of choice for patients with end-stage renal disease. With improvements in immunosuppression, graft and patient outcomes have significantly improved. However, with the more widespread use of induction therapy and more potent immunosuppressants, BKV has become recognized as an important complication after kidney transplantation.[3]

The first case of BKV infection in a kidney transplant recipient was reported in 1971.[4] Two human polyomaviruses were isolated and named after the patients in whom they were first identified. BKV was found in the urine of a kidney transplant recipient. In the era of cyclosporine-based immunosuppression, BKV was rarely of clinical significance. With the use of more potent drugs such as tacrolimus and mycophenolate mofetil (MMF), incidence of BKV in kidney transplant recipients has increased, although some conflicting data exist. The unique feature of BKV infection in kidney transplant recipients is the lack of fever, malaise, leukopenia, anemia or other signs and symptoms typical of viral infection. Reactivation of BKV post kidney transplant is common during the first year with a prevalance of 45% to 50%.[5] It occurs mostly within the first three months of transplant.

The risk of BKVN increases when viral load in the urine is greater than 10^7 copies/mL or viral load in the plasma is greater than 10^4 copies/mL.[6] BKVN occurs in 1%-5% of kidney transplant patients with graft loss in approximately 10%-30% of cases.[7,8] The diagnosis of BKVN can only be made histologically by graft kidney biopsy. The development of BKVN appears to follow asymptomatic reactivation of BK virus in the urine. More transplant centers have recently reported prospective monitoring of BK viruria by using polymerase chain reaction (PCR) studies.[9]

Methods

Since August 2008, we started to prospectively monitor for BK viruria monthly during the first three months for all kidney transplant recipients performed at Hawai'i Medical Center East. When urine BK viral load was greater than 10^7copies/mL, plasma BKV load was also tested. If the recipient was found to be BK viremic, MMF or calcineurin inhibitors were reduced. If concomitant serum creatinine was elevated, transplant kidney biopsy was considered.

All patients received an induction immunosuppression with 3 mg/kg of daclizumab in two divided doses. In cases of delayed graft function, rabbit antithymocyte globulin was considered. Maintenance immunosuppression consisted of calcineurin inhibitors (cyclosporine or tacrolimus), MMF and corticosteroids. MMF was started at 1 g twice daily and adjusted thereafter. Methyprednisolone was given 500 mg intravenously in the operating room and then tapered to oral prednisone until a maintenance dose of 2.5 to 5 mg/day was achieved. Acute rejection was treated with steroid pulses first. Rabbit antithymocyte globulin was given for acute rejections unresponsive to steroids.

Results

From August 2008 through May 2009, a total of 28 kidney transplants were performed at Hawai'i Medical Center East in Honolulu. Characteristics of the recipients are described in Table 1. One patient died from cerebrovascular accident perioperatively. One patient deferred BKV monitoring due to financial reasons. Among the remaining 26 patients, three developed positive BKV load in the urine. All three of these patients were found to have BK viremia. The incidence was 12%. None of these patients had a concomitant elevated serum creatinine. Characteristics of these patients with positive BK viremia are described in Table 2. Immunosuppression was reduced as described until the virus cleared. Biopsy was not performed since their graft functions remained stable.

Table 1.— Characteristics of 28 Kidney Transplant Recipients

Demographics:	
Gender	Male 12: Female 16
Age (mean)	41 years (range 4-72)
Causes of End-stage Renal Disease:	
Diabetes mellitus	7 (25%)
Hypertension	5 (17.9%)
Polycystic kidney disease	4 (14.3%)
Lupus nephritits	4 (14.3%)
Chronic glomerulonephritis	3 (10.7%)
Others	5 (17.9%)
Donor Type:	
Living donor	9 (32.1%)
Deceased donor	19 (67.9%)

Table 2.— Characteristics of three patients with positive BKV							
	Causes of ESRD	**Donor type**	**Induction therapy**	**Maintenance therapy**	**Treatment**	**Response to treatment**	**Biopsy**
40 M	Lupus nephritis	LU	daclizumab	CSA, MMF, Pre	Reduction of MMF	Yes	No
36 F	Hypertension	D	daclizumab	CSA, MMF, Pre	Reduction of MMF	Yes	No
15 F	CIT	LR	daclizumab	TAC, MMF, Pre	Reduction of TAC	Yes	No

ESRD = end-stage renal disease, CIT = calcineurin inhibitor toxicity, LU = living unrelated, D = deceased, LR = living related, CSA = cyclosporine, TAC = tacrolimus, MMF = mycophenolate mofetil, Pre = prednisone

Table 3.— Comparison of BK (+) patients and BK(-) patients		
	BK + (n=3)	**BK - (n=23)**
Age, years (mean)	15-40 (30)	4-73 (52)
Gender		
Male	1 (67%)	10 (43%)
Female	2 (33%)	13 (57%)
Donor type		
Deceased donor	1 (33%)	16 (70%)
Living donor	2 (67%)	7 (30%)
Induction therapy		
Daclizumab	3 (100%)	23 (100%)
Antithymocyte globulin	0 (0%)	0 (0%)
Calcineurin inhibitors		
Cyclosporine	2 (67%)	14 (61%)
Tacrolimus	1 (33%)	9 (39%)
Acute rejection	0 (0%)	2 (9%)
Delayed graft function	0 (0%)	3 (13%)

Three patients in the BK (-) group developed delayed graft function with an incidence of 13%, whereas none of the BK (+) group developed delayed graft function. Two patients in the BK (-) group had an episode of acute cellular rejection (9%) and were successfully treated with steroid bolus. No patients in the BK (+) group had an acute rejection. During the short observed postoperative period no graft was lost except for one cerebrovascular death.

Discussion

This single-center prospective study, although preliminary and small in size, showed the incidence of BK viremia (12%) in screened kidney transplant recipients in Hawai'i. Almeras et al, reported a similar result. Their incidence of BK viremia in 123 prospectively monitored kidney transplant recipients during the first year was 10.5%.[10] Similar results were reported by other centers. Hirsch et al[11] reported an incidence of 13 % among their 78 kidney transplant recipients. Brennan et al[12] reported an incidence of 11.5% among 200 patients.

The management of BKV after kidney transplantation is challenging. Diagnosis tends to be made late in its clinical course due to lack of specific symptoms and perhaps inadequate recognition by transplant clinicians. Treatment is difficult because antiviral treatment is ineffective and too rapid reduction of immunosuppression can trigger acute rejection. At present, the principal treatment is reduction of immunosuppression until the virus clears. Once BKVN develops, graft loss is common. Therefore, early detection is crucial to stopping progression of the disease and subsequent graft loss. Plasma and urine PCR testing have been adopted by a number of transplant centers to screen and monitor viral presence and clearance.

There is no universally accepted screening program. Intensity of surveillance differs from program to program. We decided to screen monthly for the first three months in order not to miss any early viral reactivation and disease progression which could be missed by less frequent surveillance.[10] Due to small sample size and short follow up, no meaningful statistical analysis was made. In addition, it is to be seen whether this screening has any impact on incidence of BKVN and graft survival in the future.

Conclusion

Since August 2008, we started to prospectively screen urine and plasma BKV load for all kidney transplant patients. Although this is still preliminary, we report the incidence of BKV in our kidney transplant patients after our institutional monitoring protocol was adopted. With this approach, we hope the incidence of BKVN and subsequent graft loss can be lowered by early viral detection and optimal management of immunosuppresion.

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Liver Transplant Referrals: The Burden of End-Stage Liver Disease in Hawai'i

Linda L. Wong MD; Naoky Tsai MD; Tarun Sharma MD; Makoto Ogihara MD; Chet Hammill MD; and Jane Lee RN

Abstract

Liver transplantation, a treatment for end-stage liver disease and fulminant hepatic failure, has been successfully performed in Hawaii since 1993. The aim of this study is to review 516 patients who were referred for possible liver transplant between 1999 and 2008 and compare characteristics of patients referred 1999-2003 (group 1) to those referred 2004-2008 (group 2). Chronic viral hepatitis C was the most frequent cause of liver disease for which evaluation was considered. More patients were referred in group 2 (n=325) compared to group 1 (n=191). Patients referred in group 2 had similar demographics and disease etiology but were more likely to have hypertension, higher prothrombin time and higher Model for End Stage Liver Disease (MELD) score. There was no difference between the groups in the proportion that were evaluated for liver transplant, placed on the list, or eventually underwent transplant.

Introduction

The first liver transplant (LT) in Hawai'i was performed on May 1993.[1] Since that time nearly 150 LT have been successfully performed with results comparable to mainland programs. We initially reported our first five-year experience with 21 cases.[2] The first 100 cases were summarized and demonstrated a 1 and 5 year survival rates of 89% and 71% respectively. The authors have demonstrated that a small-volume liver transplant center can survive and perform comparable to larger centers, if special efforts are made to maintain skills with complex hepatobiliary surgery and renal transplant.[3]

The United Network for Organ Sharing (UNOS) maintains a database of statistics on all solid organ transplants. The 2008 Annual Report from the Scientific Registry of Transplant Recipients (SRTR) affiliated with UNOS indicated that liver transplant was primarily done for viral hepatitis B and C (HBV, HCV) with smaller proportions done for cholestatic disorders, fulminant hepatic failure, metabolic disorders and malignancies. Associated hepatocellular cancer (HCC) is becoming more prevalent as liver physicans have found better ways to sustain these patients with chronic liver disease. Currently 10.4% of all patients transplanted in the United States have known HCC or incidentally found HCC on the explanted liver.[4] The goal of this study is to describe nature of end-stage and fulminant liver disease in Hawai'i as determined by referrals to our center for possible liver transplant.

Methods

This is a retrospective study of patients who were referred to the liver transplant team of the Transplant Institute at Hawaii' Medical Center – East (formerly St. Francis Medical Center) for evaluation for possible LT between January 1, 1999 and December 31, 2008. Records were reviewed for demographic information including age, gender, ethnicity, and birthplace. Referring physician specialty (gastroenterology, internal/family medicine, oncology, surgery or Liver Center physician) and island of origin were noted. We then identified the etiology of end-stage liver disease (ESLD), risk factors and co-morbidities including the presence of diabetes mellitus (DM), hypertension, cardiac disease, previous malignancy, HCC, alcohol use, and smoking. Laboratory data collected included serum bilirubin, albumin, prothrombin time, creatinine and platelet count. The presence of ascites and encephalopathy were noted to calculate a Childs-Turcotte Pugh score (CTP). CTP scores range from 5-15 and were previously used for allocation. Bilirubin, prothrombin time and creatinine were used to calculate a Model for End-Stage Liver Disease (MELD) score. Each patient's insurance status was categorized into: Private, Medicaid/State, Medicare or none.

Finally, it was noted whether each patient underwent the complete evaluation for transplant, was listed and eventually underwent liver transplant. Reasons for not undergoing or completing the evaluation were categorized into; (1) Medical (advanced cardiopulmonary disease, active malignancy, active infection, morbid obesity or other medical comorbidities); (2) Too early; (3) Psychosocial (active substance abuse, noncompliance, poorly controlled psychiatric disease, or absence of a primary caregiver); (4) Financial; or (5) Other (patient desire to pursue liver transplant in another center, refusal, or incomplete evaluation).

Data was then compiled into 2 eras: 1999-2003 and 2004-2008. Mean age, bilirubin, albumin, prothrombin time, platelet count, CTP score, and MELD score were calculated and compared using the Students t-test. Differences in the etiology of ESLD, co-morbidities and outcome (LT evaluation, listing, and transplant) were compared using the Fisher exact test.

Results

During the 10-year period (1999-2008), 516 patients were referred for LT evaluation. Mean age was 52.5 years with range 18 to 83 years. Male: female ratio was 330:181. Ethnic distribution was as follows: Caucasian – 221 (42.8%), Asian – 189 (36.6%), Pacific Islander – 40 (8.5%), Mixed-36 (7.0%), Hispanic – 19 (3.7%), African-American -8(1.6%) , unknown – 4 (0.8%). Of the Asian patients, specific distribution was as follows: Japanese – 96, Chinese – 31, Korean – 29, Filipino – 25, Vietnamese – 6, and Thai – 2.

The year of referral was as noted in Table 1. Most patients were referred from physicians on O'ahu (n = 396), with fewer patients originating from the Big Island (n = 55), Maui (n = 33), Kaua'i (n = 18), and Lana'i (n = 3). Patients on neighboring islands frequently had physicians on their own island but were referred by consulting physicians on O'ahu. Most patients were referred by local gastroenterologists (n = 196) or the physicians at Hawai'i Medical Center-East Liver Center (n = 124). Patients were also referred by internal medicine physicians (n=172), oncologists (n=11), and surgeons (n=3).

Over 60% of the patients referred for LT had some type of chronic viral hepatitis. More patients had HCV (n=235) than HBV (n=76) and 2 patients were coinfected. Table 2 shows the complete list of disease etiologies. Of those with HCV, identified risk factors included: prior intravenous drug use (n=92), blood transfusions

Table 1.— Number of referrals by year	
Year	**Number of referrals**
1999	28
2000	48
2001	41
2002	26
2003	47
2004	72
2005	65
2006	67
2007	55
2008	66

Table 2.— Etiology of ESLD	
Disease etiology	**Number of patients**
Hepatitis C	235
Hepatitis B	76
HBV/HCV co infection	2
Alcohol	70
Nonalcoholic steatosis	45
Acute liver failure	20
Primary biliary cirrhosis	19
Cryptogenic cirrhosis	12
Autoimmune hepatitis	9
Primary sclerosing cholangitis	5
Polycystic liver disease	4
Budd Chiari	2
Biliary Atresia	2
Second Biliary Cirrhosis	2
Wilsons disease	2
Hemachromatosis	2
Other	5
Unknown	3

(n=35), intranasal cocaine (n=12), and tattoos (n=11). In 26 other patients one of the following risk factors were identified: multiple injections in the military, promiscuous sexual activity, acupuncture, surgery many years prior, prison employment, needlestick injury as a health care worker, and spouse with HCV. Risk factors for HBV were mostly unknown. Twenty of the 76 patients with HBV had vertical transmission suggested with at least one other immediate relative with HBV.

Of 20 patients with acute or fulminant hepatitis, specific etiologies included: drug-induced (n=8), HBV (n=7), autoimmune hepatitis (n=1), Wilson's disease (n=1), and unknown (n=3). Specific drugs responsible for acute liver failure included: isoniazid- 2, non-steroidal anti-inflammatory drugs – 2, antibiotics – 2, Usnic acid – 1, and acetaminophen – 1. Although there were many more acetaminophen toxicity cases, these were usually inpatient referrals and patients recovered quickly without consideration for formal LT evaluation.

In these 516 patients referred, other medical co-morbidities were frequently noted. These included: hypertension- 143 (27.7%), DM - 123 (23.8%), and cardiovascular disease- 35 (6.8%). Seventy-six (14.7%) patients were documented as being obese though BMI was not consistently recorded in early years. In terms of neoplasm, 84 (16.3%) patients had HCC with their chronic liver disease and 35 patients had a history of a non-HCC cancer. In terms of personal habits, 272 patients had a history of smoking and 275 patients had a history of alcohol use.

Patients were referred with mean bilirubin 3.55 mg/dL, albumin 3.05 g/dL, protime 16.5 seconds with INR 1.30, creatinine 1.01 mg/dL, and platelet count 106,700/cc. At referral, mean CTP score was 8.3 and mean MELD score was 14.0. Of 442 patients who had known insurance status, 318 had private insurance, 102 patients had Medicaid, and 22 had Medicare.

In the 516 referred patients, 262 were formally evaluated, 199 were eventually listed, and 116 underwent LT. Of the 199 patients placed on the transplant waiting list, 41 continue to remain currently on the list, 28 died while waiting for a liver, and 14 patients were inactivated (progression of HCC, sepsis, noncompliance, or relocation to the Mainland).

Of the 317 patients who were not listed after evaluation or not evaluated at all, 85 patients were not candidates due to psychosocial reasons. Most of these reasons were multifactorial involving inadequate social support system, noncompliance with medical care, active alcohol or substance abuse and/or refusal to complete the evaluation process. Nine patients refused to undergo evaluation. (See Figure 1)

Seventy-two patients were deemed non-transplant candidates due to medical reasons. Most of these patients (n=19) were not candidates for multiple medical co-morbidities or being too ill at the time of referral. Specific isolated problems listed in other patients included: morbid obesity - 16, too extensive HCC - 11, age - 10, HIV positivity - 5, extensive cardiac problem - 4, new cancer identified during evaluation - 3, pulmonary hypertension - 3, and other - 1.

Of the 317 patients who were not candidates, an additional 56 were felt to be too early for formal LT evaluation, 10 had financial issues and 9 are currently undergoing evaluation. Sixty-five patients had incomplete information available at the time of this study.

In comparing patients from the 1999-2003 to 2004-2008 eras, data are summarized in Table 3. There was no difference in demographics or comorbidities except a larger proportion of patients in the more recent era had hypertension. Patients in the 2004-2008 era had higher prothrombin times and INR, and were referred with a higher MELD score suggesting that patients who were referred were sicker. There was no difference between the groups in terms of patients evaluated, listed or transplanted.

Discussion

Proper referral for evaluation is essential for optimal outcome for patients with chronic liver disease and fulminant liver failure who may qualify for LT. The basic goal of the transplant evaluation is to determine if a patient has any absolute or relative contraindications to LT and to decide on proper timing for placement on the transplant waiting list. Absolute contraindications would include: active substance abuse, inadequate cardiopulmonary function to tolerate a prolonged surgical procedure, metastatic or active cancer (other

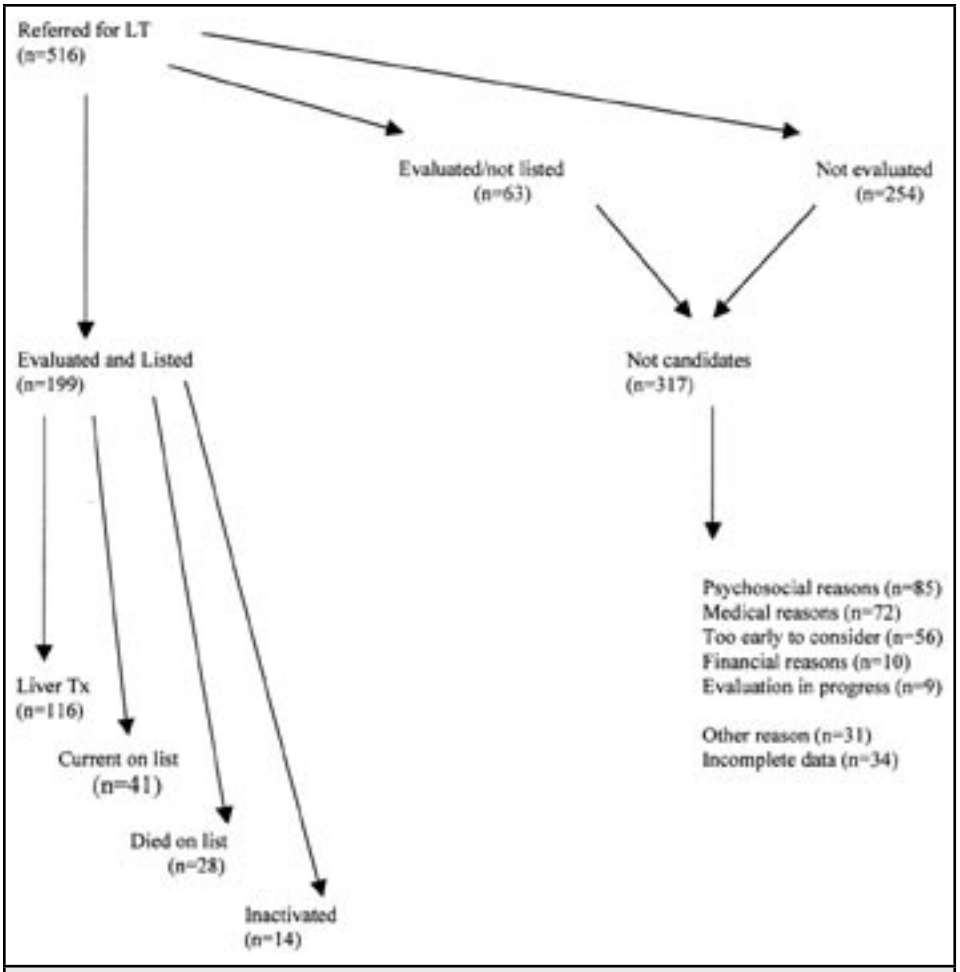

Figure 1.— Outcome of Patients referred for liver transplant

than a small HCC), active infection, current substance abuse, or insufficient psychosocial support system to assist with the transplant and assure compliance. It is important that the primary care physician be able to recognize the underlying features of these diseases and determine if referral to a transplant center is warranted.

Viral hepatitis

HBV and HCV account for 61% of patients referred for transplant evaluation at our center. This may be due to the maturation of the HCV epidemic which occurred in the 1960's and 1970s. The prevalence of cirrhosis and its complications in this subset of patients is only expected to increase over the next 10-15 years.[5] HBV appears to be a particularly prevalent problem for Hawai'i, as a recent study by our group showed a ten fold higher prevalence rate (3.5% vs 0.3%) compared to the rest of the United States.[6] Early identification of viral hepatitis is important as treatment of HBV and HCV prior to decompensation may prevent or delay the need for LT.

Substance Abuse

Alcohol or illicit drug use is frequently a complicating factor in ESLD and most centers including ours require six months of abstinence before evaluation. Everhart et al. determined that 85% of LT programs in United States and 43% of third party payers require 3-6 months of abstinence.[7] A prospective study of 51 patients transplanted for alcoholic liver disease concluded that abstinence before LT was the only predictive factor of alcohol relapse post LT.[8] On the other hand, another study found the length of pre-transplant abstinence to be a poor predictor of post transplant abstinence.[9] Patients who relapse also have worse 10-year survival and deaths are frequently due to cancer and cardiovascular disease.[10]

Obesity/Non-Alcoholic Steatohepatitis (NASH)

Obesity and the associated features of the metabolic syndrome are rapidly becoming an epidemic in the United States. More patients with NASH are being referred for LT, however the associated comorbidities need to be carefully evaluated. Obesity and especially morbid obesity can pose physical as well as logistic problems for LT. These patients are more prone to wound problems, infections, and difficulty with imaging procedures. Finding appropriately-sized matched donor organs that do not have fatty changes can also be problematic. Evidence on the impact of obesity in patients undergoing LT remains controversial. One study noted an 11% and 29% lower chance of receiving LT in patients with severe and morbid obesity respectively.[11] Hasse et al noted decreased short and long term survival in morbidly obese LT recipients.[12] We thus encourage weight reduction/exercise in patients with a BMI > 35 since this is a recommendation from American Asssociation for the Study of Liver Disease (AASLD) practice guidelines for evaluation of patients undergoing LT.[13]

Hepatocellular Cancer

Hawai'i has the highest incidence (10.3/100,000) and death rate (7.9/100,000) of HCC in the United States.[14] LT is the best treatment for long-term disease free survival in limited HCC. LT is considered for HCC that meet Milan criteria (single nodule < 5 cm or up to 3 nodules, all <3 cm). The initial study demonstrated 83% recurrence-free 4-year survival based on this criteria.[15] More recent studies from UCSF have suggested that mild extension of the criteria and use of radiofrequency ablation or chemoembolization to downstage the tumors to Milan criteria, can yield similarly good results.[16] Screening patients with viral hepatitis to allow early identification of HCC may afford patients the best opportunity for treatment with LT.

Liver Allocation

It is important that primary care physicians be familiar with the MELD system for organ allocation. AASLD guidelines recommend that patients with chronic liver disease should be referred to LT center when MELD ≥ 10 or CTP > 7 or if they have a major complication (encephalopathy, variceal bleed or ascites).[16] MELD score is defined as 3.8 x

log (e) (bilirubin mg/dL) + 11.2 x log (e) (INR) + 9.6 log (e) (creatinine mg/dL). (Calculators are available for this at www.unos.org) MELD scores range from 7 to 40 and liver are allocated to highest MELD scores first. CTP score is no longer used in allocation due to inaccuracy in reporting of subjective values such as encephalopathy and ascites, but is sometimes easier for the referring physician in the office setting. Our data would suggest that some patients are being referred for a LT with a higher MELD score or at times too early for the formal transplant evaluation. While the actual evaluation and listing will occur under the direction of the transplant team, the primary care physician can be essential in proper referral and management to assure evaluation and perhaps even delay the need for LT.

This study is limited in that it covered primarily outpatient evaluations and not all inpatient evaluations may have been included especially if they were seen by the transplant team and found to have an absolute contraindication early in assessment. Many neighbor island inpatients who were referred via telephone by primary care physicians and determined to be too unstable for transport or clearly inappropriate for LT were excluded. Finally although members of the transplant team may have seen many more acetaminophen overdoses, a large number of these recovered rapidly and were not included in this analysis.

Conclusion

The LT program at the HMC-East continues to perform at the same level of excellence as other US programs despite the smaller volume. Appropriate evaluation/pre-transplant management and life-long follow-up of our transplanted patients have contributed to our success. Our data indicate that referrals are increasing and the community support from our referring physicians has been overwhelming. This is the backbone of our success. The people of Hawai'i truly benefit from this program for without it they would have to travel to mainland centers at a greater financial cost and be without their complete psychosocial support system during the time of greatest need. Many patients would be too ill to survive the transport and more would die without LT. With a skillful surgical team, a dedicated Liver Center with expertise, experienced consulting physicians, and a tremendous support staff of nurse coordinators, social workers, and coordinators, a high level of performance can be maintained even in a small LT program.

Acknowledgements

It has been a extraordinary journey to bring liver transplant to the people of Hawai'i and we thank our referring physicians for this opportunity.

Table 3.— Characteristics of patients 1999-2003 vs 2004-2008

	1999-2003	2004-2008	p
# patients	191	325	
Mean age (years)	52.1	52.7	NS
Men: Women	128:63	204:119	NS
Asian/Pacific Islander	107	160	NS
NonAsian	84	165	
Diabetes	49 (25.7%)	74 (22.9%)	NS
Hypertension	41(21.6%)	101(31.4%)	p=0.02
Cardiac disease	13 (6.8%)	22 (6.8%)	NS
Obesity	22(11.5%)	46 (17.2%)	NS
Hepatocellular Cancer	32 (16.9%)	51 (16.9%)	NS
Alcohol history	94 (49.7%)	177 (55.1%)	NS
Smoking history	103 (55.1%)	171 (53.9%)	NS
Hepatitis C	76 (39.8%)	159 (48.9%)	NS
Hepatitis B	34 (17.8%)	42 (12.9%)	NS
Acute liver failure	5 (2.6%)	15 (4.6%)	NS
Bilirubin (mg/dL)	3.1	3.8	NS
Albumin (g/dL)	3.0	3.1	NS
Protime (sec)	15.4	17.1	p=0.00003
INR	1.09	1.42	p<0.0001
Creatinine (mg/dL)	1.04	1.00	NS
Platelet Count (x103)	103.8	108.4	NS
MELD score	12.3	14.2	p=0.00002
Insurance			
Private	119 (75.3%)	205 (70.0%)	NS
Medicaid	27 (17.2%)	76 (25.9%)	
Medicare	12 (7.6%)	11 (3.8%)	
Unknown/None	33 (17.3%)	32 (9.8%)	

Table 4.— Summary of Recommendations

1. Screen for HBV/HCV - all patients who received blood transfusions prior to 1992, close contacts of patients with HBV/HCV, Asian immigrants, and patients with high risk sexual behavior, intravenous drug use, intranasal cocaine use, or tattoos. Screen all patients for HBV prior to chemotherapy/immunotherapy as these drugs can reactivatee HBV.
2. Provide counseling and resources for patients with ongoing substance abuse.
3. Encourage weight reduction/exercise in patients with a BMI > 35.
4. Use MELD score to evaluate patients with ESLD. Refer if MELD >10 or with suspected hepatorenal syndrome.
5. Screen for HCC. While awaiting evaluation all high risk patients should undergo surveillance for hepatocellular carcinoma with an AFP level every 3 months and an imaging (ultrasound or CT scan) every 6 months.
6. Refer early if hepatotoxicity is suspected. In case of suspected drug toxicity the offending agent must be withdrawn at the earliest and timely referral for LT initiated in those who continue to deteriorate.

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Dr. Arnold Siemsen and surgeon, Dr Livingston Wong in 1969 in the operating room, awaiting transplant surgery.

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INDICATION AND USAGE

VIREAD® (tenofovir disoproxil fumarate) is indicated for the treatment of chronic hepatitis B in adults.

The following points should be considered when initiating therapy with VIREAD for the treatment of HBV infection:

- This indication is based on data from one year of treatment in primarily nucleoside-treatment-naïve adult patients with HBeAg-positive and HBeAg-negative chronic hepatitis B with compensated liver disease
- The numbers of patients in clinical trials who were nucleoside-experienced or who had lamivudine-associated mutations at baseline were too small to reach conclusions of efficacy
- VIREAD has not been evaluated in patients with decompensated liver disease

WARNINGS: LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS and POST TREATMENT EXACERBATION OF HEPATITIS

- **Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including VIREAD, in combination with other antiretrovirals**
- **Severe acute exacerbations of hepatitis have been reported in HBV-infected patients who have discontinued anti-hepatitis B therapy, including VIREAD. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue anti-hepatitis B therapy, including VIREAD. If appropriate, resumption of anti-hepatitis B therapy may be warranted**

Please see continued Important Safety Information for VIREAD on adjacent page.

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WARNINGS AND PRECAUTIONS

- New onset or worsening renal impairment: Can include acute renal failure and Fanconi syndrome. Assess creatinine clearance (CrCl) before initiating treatment with VIREAD. Monitor CrCl and serum phosphorus in patients at risk. Avoid administering VIREAD with concurrent or recent use of nephrotoxic drugs, including HEPSERA® (adefovir dipivoxil)
- Products with same active ingredient: Do not use with other tenofovir-containing products (e.g., ATRIPLA® (efavirenz/emtricitabine/tenofovir disoproxil fumarate) and TRUVADA® (emtricitabine/tenofovir disoproxil fumarate))
- VIREAD should not be administered in combination with HEPSERA
- HIV testing: HIV antibody testing should be offered to all HBV-infected patients before initiating therapy with VIREAD. VIREAD should only be used as part of an appropriate antiretroviral combination regimen in HIV-infected patients with or without HBV coinfection
- Decreases in bone mineral density (BMD): Observed in HIV-infected patients. Consider monitoring BMD in patients with a history of pathologic fracture or who are at risk for osteopenia. The bone effects of VIREAD have not been studied in patients with chronic HBV infection

DRUG INTERACTIONS

- Didanosine: Coadministration increases didanosine concentrations. Use with caution and monitor for evidence of didanosine toxicity (e.g., pancreatitis, neuropathy). Didanosine should be discontinued in patients who develop didanosine-associated adverse reactions. In adults weighing >60 kg, the didanosine dose should be reduced to 250 mg when it is coadministered with VIREAD. Data are not available to recommend a dose adjustment of didanosine for patients weighing <60 kg
- Atazanavir: Coadministration decreases atazanavir concentrations and increases tenofovir concentrations. Use atazanavir with VIREAD only with additional ritonavir; monitor for evidence of tenofovir toxicity
- Lopinavir/ritonavir: Coadministration increases tenofovir concentrations. Monitor for evidence of tenofovir toxicity

ADVERSE REACTIONS

- In HBV-infected patients: Most common adverse reaction (all grades) was nausea (9%). Other treatment-emergent adverse reactions reported in >5% of patients treated with VIREAD included: abdominal pain, diarrhea, headache, dizziness, fatigue, nasopharyngitis, back pain, and skin rash

DOSAGE AND ADMINISTRATION

- Recommended dose for the treatment of chronic hepatitis B: 300 mg once daily taken orally without regard to food. In the treatment of chronic hepatitis B, the optimal duration of treatment is unknown
- Dose recommended in renal impairment:

  Creatinine clearance 30-49 mL/min: 300 mg every 48 hours

  Creatinine clearance 10-29 mL/min: 300 mg every 72 to 96 hours

  Hemodialysis: 300 mg every 7 days or after approximately 12 hours of dialysis

  The pharmacokinetics of tenofovir have not been evaluated in non-hemodialysis patients with creatinine clearance <10 mL/min; therefore, no dosing recommendation is available for these patients

Please see adjacent page for brief summary of full Prescribing Information for VIREAD, including ***boxed WARNINGS.***

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tenofovir disoproxil fumarate

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Brief summary of full prescribing information. Please see full prescribing information including Boxed WARNINGS. Rx only

WARNINGS: LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS and POST TREATMENT EXACERBATION OF HEPATITIS
- **Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including VIREAD, in combination with other antiretrovirals *(See Warnings and Precautions).***
- **Severe acute exacerbations of hepatitis have been reported in HBV-infected patients who have discontinued anti-hepatitis B therapy, including VIREAD. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue anti-hepatitis B therapy, including VIREAD. If appropriate, resumption of anti-hepatitis B therapy may be warranted *(See Warnings and Precautions).***

INDICATIONS AND USAGE: VIREAD is indicated for the treatment of chronic hepatitis B in adults. The following points should be considered when initiating therapy with VIREAD for the treatment of HBV infection:
- This indication is based on data from one year of treatment in primarily nucleoside-treatment-naïve adult patients with HBeAg-positive and HBeAg-negative chronic hepatitis B with compensated liver disease.
- The numbers of patients in clinical trials who were nucleoside experienced or who had lamivudine-associated mutations at baseline were too small to reach conclusions of efficacy.
- VIREAD has not been evaluated in patients with decompensated liver disease.

DOSAGE AND ADMINISTRATION: For the treatment of chronic hepatitis B, the dose of VIREAD is 300 mg once daily taken orally, without regard to food. The optimal duration of treatment is unknown. **Dose Adjustment for Renal Impairment:** Significantly increased drug exposures occurred when VIREAD was administered to patients with moderate to severe renal impairment. Therefore, the dosing interval of VIREAD should be adjusted in patients with baseline creatinine clearance <50 mL/min using the recommendations in Table 1. These dosing interval recommendations are based on modeling of single-dose pharmacokinetic data in non-HIV and non-HBV infected subjects with varying degrees of renal impairment, including end-stage renal disease requiring hemodialysis. The safety and effectiveness of these dosing interval adjustment recommendations have not been clinically evaluated in patients with moderate or severe renal impairment, therefore clinical response to treatment and renal function should be closely monitored in these patients *(See Warnings and Precautions)*. No dose adjustment is necessary for patients with mild renal impairment (creatinine clearance 50–80 mL/min). Routine monitoring of calculated creatinine clearance and serum phosphorus should be performed in patients with mild renal impairment *(See Warnings and Precautions)*.

Table 1.
Dosage Adjustment for Patients with Altered Creatinine Clearance

	Creatinine Clearance (mL/min)[a]			Hemodialysis Patients
	≥50	30–49	10–29	
Recommended 300 mg Dosing Interval	Every 24 hours	Every 48 hours	Every 72 to 96 hours	Every 7 days or after a total of approximately 12 hours of dialysis[b]

a. Calculated using ideal (lean) body weight.
b. Generally once weekly assuming three hemodialysis sessions a week of approximately 4 hours duration. VIREAD should be administered following completion of dialysis.

The pharmacokinetics of tenofovir have not been evaluated in non-hemodialysis patients with creatinine clearance <10 mL/min; therefore, no dosing recommendation is available for these patients.

CONTRAINDICATIONS: None.

WARNINGS AND PRECAUTIONS: Lactic Acidosis/Severe Hepatomegaly with Steatosis: Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs alone or in combination with other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering nucleoside analogs to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with VIREAD should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations). **Exacerbation of Hepatitis after Discontinuation of Treatment:** Discontinuation of anti-HBV therapy, including VIREAD, may be associated with severe acute exacerbations of hepatitis. Patients infected with HBV who discontinue VIREAD should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, resumption of anti-hepatitis B therapy may be warranted. **New Onset or Worsening Renal Impairment:** Tenofovir is principally eliminated by the kidney. Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported with the use of VIREAD *(See Adverse Reactions)*. It is recommended that creatinine clearance be calculated in all patients prior to initiating therapy and as clinically appropriate during therapy with VIREAD. Routine monitoring of calculated creatinine clearance and serum phosphorus should be performed in patients at risk for renal impairment. Dosing interval adjustment of VIREAD and close monitoring of renal function are recommended in all patients with creatinine clearance <50 mL/min *(See Dosage and Administration)*. No safety or efficacy data are available in patients with renal impairment who received VIREAD using these dosing guidelines, so the potential benefit of VIREAD therapy should be assessed against the potential risk of renal toxicity. VIREAD should be avoided with concurrent or recent use of a nephrotoxic agent. **Coadministration with Other Products:** VIREAD should not be used in combination with the fixed-dose combination products TRUVADA® (emtricitabine/tenofovir disoproxil fumarate) or ATRIPLA® (efavirenz/emtricitabine/tenofovir disoproxil fumarate) since tenofovir disoproxil fumarate is a component of these products. VIREAD should not be administered in combination with HEPSERA® (adefovir dipivoxil) *(See Drug Interactions)*.

Patients Coinfected with HIV-1 and HBV: Due to the risk of development of HIV-1 resistance, VIREAD (tenofovir disoproxil fumarate) should only be used in HIV-1 and HBV coinfected patients as part of an appropriate antiretroviral combination regimen. HIV-1 antibody testing should be offered to all HBV-infected patients before initiating therapy with VIREAD. It is also recommended that all patients with HIV-1 be tested for the presence of chronic hepatitis B before initiating treatment with VIREAD. **Decreases in Bone Mineral Density:** Bone mineral density (BMD) monitoring should be considered for patients who have a history of pathologic bone fracture or are at risk for osteopenia. Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation may be beneficial for all patients. If bone abnormalities are suspected then appropriate consultation should be obtained. In HIV-infected patients treated with VIREAD in Study 903 through 144 weeks, decreases from baseline in BMD were seen at the lumbar spine and hip in both arms of the study. At Week 144, there was a significantly greater mean percentage decrease from baseline in BMD at the lumbar spine in patients receiving VIREAD + lamivudine + efavirenz (-2.2% ± 3.9) compared with patients receiving stavudine + lamivudine + efavirenz (-1.0% ± 4.6). Changes in BMD at the hip were similar between the two treatment groups (-2.8% ± 3.5 in the VIREAD group vs. -2.4% ± 4.5 in the stavudine group). In both groups, the majority of the reduction in BMD occurred in the first 24–48 weeks of the study and this reduction was sustained through Week 144. Twenty-eight percent of VIREAD-treated patients vs. 21% of the stavudine-treated patients lost at least 5% of BMD at the spine or 7% of BMD at the hip. Clinically relevant fractures (excluding fingers and toes) were reported in 4 patients in the VIREAD group and 6 patients in the stavudine group. In addition, there were significant increases in biochemical markers of bone metabolism (serum bone-specific alkaline phosphatase, serum osteocalcin, serum C-telopeptide, and urinary N-telopeptide) in the VIREAD group relative to the stavudine group, suggesting increased bone turnover. Serum parathyroid hormone levels and 1,25 Vitamin D levels were also higher in the VIREAD group. Except for bone-specific alkaline phosphatase, these changes resulted in values that remained within the normal range. The effects of VIREAD-associated changes in BMD and biochemical markers on long-term bone health and future fracture risk are unknown. Cases of osteomalacia (associated with proximal renal tubulopathy and which may contribute to fractures) have been reported in association with the use of VIREAD *(See Adverse Reactions)*. The bone effects of VIREAD have not been studied in patients with chronic HBV infection.

ADVERSE REACTIONS: Clinical Trials in Patients with Chronic Hepatitis B: Treatment-Emergent Adverse Reactions: In controlled clinical trials in patients with chronic hepatitis B, more patients treated with VIREAD experienced nausea: 9% with VIREAD versus 2% with HEPSERA (adefovir dipivoxil). Other treatment-emergent adverse reactions reported in >5% of patients treated with VIREAD included: abdominal pain, diarrhea, headache, dizziness, fatigue, nasopharyngitis, back pain, and skin rash. Grade 3/4 laboratory abnormalities identified in ≥1% of VIREAD-treated patients in studies 0102 and 0103 (0-48 weeks) included: any ≥ Grade 3 laboratory abnormality, 19%; elevated creatine kinase, 2% (M: >990 U/L; F: >845 U/L); elevated serum amylase, 4% (>175 U/L); glycosuria, 3% (urine glucose ≥3+); elevated AST, 4% (M: >180 U/L; F: >170 U/L); and elevated ALT, 10% (M: >215 U/L; F: >170 U/L). The overall incidence of on-treatment ALT elevations (defined as serum ALT >2 × baseline and >10 × ULN, with or without associated symptoms) was similar between VIREAD (2.6%) and HEPSERA (2%). ALT elevations generally occurred within the first 4–8 weeks of treatment and were accompanied by decreases in HBV DNA levels. No patient had evidence of decompensation. ALT flares typically resolved within 4 to 8 weeks without changes in study medication. **Postmarketing Experience:** The following adverse reactions have been identified during postapproval use of VIREAD. Because postmarketing reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure: allergic reaction, lactic acidosis, hypokalemia, hypophosphatemia, dyspnea, pancreatitis, increased amylase, abdominal pain, hepatic steatosis, hepatitis, increased liver enzymes (most commonly AST, ALT gamma GT), rash, rhabdomyolysis, osteomalacia (manifested as bone pain and which may contribute to fractures), muscular weakness, myopathy, acute renal failure, renal failure, acute tubular necrosis, Fanconi syndrome, proximal renal tubulopathy, interstitial nephritis (including acute cases), nephrogenic diabetes insipidus, renal insufficiency, increased creatinine, proteinuria, polyuria, asthenia. The following adverse reactions listed above, may occur as a consequence of proximal renal tubulopathy: rhabdomyolysis, osteomalacia, hypokalemia, muscular weakness, myopathy, hypophosphatemia. **DRUG INTERACTIONS: Didanosine:** Coadministration of VIREAD and didanosine should be undertaken with caution and patients receiving this combination should be monitored closely for didanosine-associated adverse reactions. Didanosine should be discontinued in patients who develop didanosine-associated adverse reactions. When administered with VIREAD, C_{max} and AUC of didanosine (administered as either the buffered or enteric-coated formulation) increased significantly. The mechanism of this interaction is unknown. Higher didanosine concentrations could potentiate didanosine-associated adverse reactions, including pancreatitis and neuropathy. Suppression of $CD4^+$ cell counts has been observed in patients receiving tenofovir disoproxil fumarate (tenofovir DF) with didanosine 400 mg daily. In adults weighing >60 kg, the didanosine dose should be reduced to 250 mg when it is coadministered with VIREAD. Data are not available to recommend a dose adjustment of didanosine for patients weighing <60 kg. When coadministered, VIREAD and didanosine EC may be taken under fasted conditions or with a light meal (<400 kcal, 20% fat). Coadministration of didanosine buffered tablet formulation with VIREAD should be under fasted conditions. **Atazanavir:** Atazanavir has been shown to increase tenofovir concentrations. The mechanism of this interaction is unknown. Patients receiving atazanavir and VIREAD should be monitored for VIREAD-associated adverse reactions. VIREAD should be discontinued in patients who develop VIREAD-associated adverse reactions. VIREAD decreases the AUC and C_{min} of atazanavir. When coadministered with VIREAD, it is recommended that atazanavir 300 mg is given with ritonavir 100 mg. Atazanavir without ritonavir should not be coadministered with VIREAD. **Lopinavir/Ritonavir:** Lopinavir/ritonavir has been shown to increase tenofovir concentrations. The mechanism of this interaction is unknown. Patients receiving lopinavir/ritonavir and VIREAD should be monitored for VIREAD-associated adverse reactions. VIREAD should be discontinued in patients who develop VIREAD-associated adverse reactions. **Drugs Affecting Renal Function:** Since tenofovir is primarily eliminated by the kidneys, coadministration of VIREAD with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of tenofovir and/or increase the concentrations of other renally eliminated drugs. Some examples include, but are not limited to cidofovir, acyclovir, valacyclovir, ganciclovir, and valganciclovir. Drugs that decrease renal function may also increase serum concentrations of tenofovir. In the treatment of chronic hepatitis B, VIREAD (tenofovir disoproxil fumarate) should not be administered in combination with HEPSERA (adefovir dipivoxil).

USE IN SPECIFIC POPULATIONS: Pregnancy: *Pregnancy Category B:* Reproduction studies have been performed in rats and rabbits at doses up to 14 and 19 times the human dose based on body surface area comparisons and revealed no evidence of impaired fertility or harm to the fetus due to tenofovir. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, VIREAD should be used during pregnancy only if clearly needed. *Antiretroviral Pregnancy Registry:* To monitor fetal outcomes of pregnant women exposed to VIREAD, an Antiretroviral Pregnancy Registry has been established. Healthcare providers are encouraged to register patients by calling 1-800-258-4263. **Nursing Mothers:** Studies in rats have demonstrated that tenofovir is secreted in milk. It is not known whether tenofovir is excreted in human milk. Because of both the potential for HIV-1 transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breast-feed if they are receiving VIREAD. Pediatric Use:** Safety and effectiveness in patients less than 18 years of age have not been established. **Geriatric Use:** Clinical studies of VIREAD did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for the elderly patient should be cautious, keeping in mind the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. **Patients with Impaired Renal Function:** It is recommended that the dosing interval for VIREAD be modified in patients with creatinine clearance <50 mL/min or in patients with end-stage renal disease (ESRD) who require dialysis *(See Dosage and Administration)*.

NONCLINICAL TOXICOLOGY: Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term oral carcinogenicity studies of tenofovir disoproxil fumarate in mice and rats were carried out at exposures up to approximately 16 times (mice) and 5 times (rats) those observed in humans at the therapeutic dose for HIV-1 infection. At the high dose in female mice, liver adenomas were increased at exposures 16 times that in humans. In rats, the study was negative for carcinogenic findings at exposures up to 5 times that observed in humans at the therapeutic dose. Tenofovir disoproxil fumarate was mutagenic in the in vitro mouse lymphoma assay and negative in an in vitro bacterial mutagenicity test (Ames test). In an in vivo mouse micronucleus assay, tenofovir disoproxil fumarate was negative when administered to male mice. There were no effects on fertility, mating performance or early embryonic development when tenofovir disoproxil fumarate was administered to male rats at a dose equivalent to 10 times the human dose based on body surface area comparisons for 28 days prior to mating and to female rats for 15 days prior to mating through day seven of gestation. There was, however, an alteration of the estrous cycle in female rats.

PATIENT COUNSELING INFORMATION: Information for Patients
Patients should be advised that:
- VIREAD is not a cure for HIV-1 infection and patients may continue to experience illnesses associated with HIV-1 infection, including opportunistic infections. Patients should remain under the care of a physician when using VIREAD.
- The use of VIREAD has not been shown to reduce the risk of transmission of HIV-1 or HBV to others through sexual contact or blood contamination.
- The long-term effects of VIREAD are unknown.
- VIREAD Tablets are for oral ingestion only.
- VIREAD should not be discontinued without first informing their physician.
- If you have HIV-1 infection, with or without HBV coinfection, it is important to take VIREAD with combination therapy.
- It is important to take VIREAD on a regular dosing schedule and to avoid missing doses.
- Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Treatment with VIREAD should be suspended in any patient who develops clinical symptoms suggestive of lactic acidosis or pronounced hepatotoxicity (including nausea, vomiting, unusual or unexpected stomach discomfort, and weakness) *(See Warnings and Precautions)*.
- Patients with HIV-1 should be tested for hepatitis B virus (HBV) before initiating antiretroviral therapy *(See Warnings and Precautions)*.
- Severe acute exacerbations of hepatitis have been reported in patients who are infected with HBV or coinfected with HBV and HIV-1 and have discontinued VIREAD *(See Warnings and Precautions)*.
- In patients with chronic hepatitis B, it is important to obtain HIV antibody testing prior to initiating VIREAD *(See Warnings and Precautions)*.
- Renal impairment, including cases of acute renal failure and Fanconi syndrome, has been reported. VIREAD should be avoided with concurrent or recent use of a nephrotoxic agent *(See Warnings and Precautions)*. Dosing interval of VIREAD may need adjustment in patients with renal impairment *(See Dosage and Administration)*.
- VIREAD should not be coadministered with the fixed-dose combination products TRUVADA (emtricitabine/tenofovir disoproxil fumarate) and ATRIPLA (efavirenz/emtricitabine/tenofovir disoproxil fumarate) since it is a component of these products *(See Warnings and Precautions)*.
- VIREAD should not be administered in combination with HEPSERA *(See Warnings and Precautions)*.
- Decreases in bone mineral density have been observed with the use of VIREAD in patients with HIV. Bone mineral density monitoring should be considered in patients who have a history of pathologic bone fracture or at risk for osteopenia *(See Warnings and Precautions)*.
- In the treatment of chronic hepatitis B, the optimal duration of treatment is unknown. The relationship between response and long-term prevention of outcomes such as hepatocellular carcinoma is not known.

For detailed information, please see full prescribing information. To learn more: call 1-800-GILEAD-5 (1-800-445-3235) or visit www.VIREAD.com.

Reference: 1. VIREAD (tenofovir disoproxil fumarate) Prescribing Information. Foster City, CA: Gilead Sciences, Inc.; November 2008.

GILEAD

Successful Consecutive Pregnancies After a Combined Pancreas-Kidney Transplant in Hawai'i

Alan H.S. Cheung MD, MBA, FACS

Abstract

Pancreas-kidney transplantation is the preferred treatment modality for selected patients with insulin-dependent diabetes mellitus and end stage renal failure. Pregnancy in women after such a transplant remains relatively uncommon. This report describes the first successful consecutive pregnancies in a woman after a combined pancreas-kidney transplant in Hawai'i. The outcomes of these two pregnancies and lessons learned are discussed.

Introduction

The first child born to a kidney transplant recipient turned 51 years old on March 10, 2009.[1] When transplantation first began, physicians were concerned about the teratogenicity of immunosuppressive medications and considered pregnancy ill-advised. Despite early concerns, more than 14,000 births among female recipients with transplanted organs have been reported worldwide.[2] Pregnancy is now considered a potential benefit for women who wish to start a family after an organ transplant.

Pancreas transplantation is a preferred treatment modality for selected patients with diabetes mellitus. The first combined pancreas and kidney transplant in Hawai'i was performed in 1993.[3] Pregnancy in women after a pancreas-kidney transplant is relatively rare. This case report describes the first successful outcome of consecutive pregnancies in a woman after a combined pancreas-kidney transplant in Hawai'i.

Case 1

The patient was a 31-year-old woman who was diagnosed with type 1 diabetes mellitus at the age 2 1/2 years and was started on insulin at that time. She later developed complications related to her diabetes including diabetic retinopathy treated with laser photocoagulation to the right eye, but caused her blindness in the left eye. She also had diabetic neuropathy with gastroparesis. She developed progressive diabetic nephropathy and chronic kidney disease stage 5 with a serum creatinine of 4 – 5 mg/dl. She was pre-dialysis and made about a liter of urine daily. In January 2000 she was evaluated and was deemed to be a reasonable candidate for a combined pancreas and kidney transplant.

She underwent a successful combined cadaveric renal and pancreas transplantation with bladder drainage of the pancreas at St. Francis Medical Center on September 10, 2000. The donor was a 31-year-old man who died from an astrocytoma of the brain. Both the transplanted kidney and pancreas functioned well after surgery. She was placed on an immunosuppressive protocol of prednisone, mycophenolate mofetil (MMF) and tacrolimus. She was discharged home on post-transplant day 14 with a serum creatinine of 0.9 mg/dl and glucose of 80 mg/dl off all insulin.

She did well a year after her transplants and wanted to start a family at that time. Her transplanted organs continued to function well without any episodes of acute rejection. In an effort to minimize potential fetotoxic drugs, her immunosuppressive regimen was changed from MMF to azathioprine, with continuation of the prednisone and tacrolimus in September 2001. By December 2001, the patient was pregnant. She was monitored closely by her transplant physicians and a high-risk pregnancy perinatologist. Her pre-natal course was complicated by hypertension, but without hyperglycemia or renal insufficiency. She developed pre-eclampsia later during her pregnancy with dangerously low amnionic fluid levels and underwent an urgent cesarean section in July 2002.

At 30 weeks, an 811 gram (1 lb., 12.6 oz.) infant girl was delivered with multiple complications of prematurity and oliguric renal insufficiency with a serum creatinine as high as 7.3 mg/dl, thought to be related to the tacrolimus. She required ventilator support for two weeks but was discharged home after two months in the hospital. She did have an atrial septal defect that required surgical closure in May 2005. This child is now nearly 7 years old and developing normally.

Postpartum the patient resumed tacrolimus and MMF in addition to prednisone. By April 2003, she wanted to have a second child. In preparation for the second pregnancy, her immunosuppressive medication was changed from tacrolimus and MMF to Gengraf (cyclosporine) and azathioprine, with continuation of her prednisone. She again became pregnant shortly after that. She did develop hypertension during the second pregnancy, but again without renal insufficiency or hyperglycemia. At 37 weeks, she delivered a healthy 2,486 gm (5 lbs., 7.7 oz.) male infant by cesarean section in November 2004. (See Table 1) This child is now healthy and developing well at 4 years of age. Postpartum the patient again resumed tacrolimus, MMF and prednisone. Her most recent serum creatinine was 1.36 mg/dl and serum glucose was 101 mg/dl.

Discussion

Information about pregnancy in recipients of solid-organ transplants comes primarily from voluntary registries, case reports, and retrospective center studies. The National Transplantation Pregnancy Registry (NTPR) was established in 1991 to study the outcomes of pregnancies in transplant recipients in North America, including female transplant recipients who have had pregnancies and male transplant recipients who have fathered pregnancies. All pregnancy outcomes are analyzed including live-births, spontaneous abortions, therapeutic abortions, stillbirths, and ectopic pregnancies. The data also include the follow-ups of parents and their offspring to determine if there are any long-term effects of pregnancy for the recipient, graft or long-term sequelae for the offspring.[4]

Most pregnancies in the NTPR database occur after kidney transplants. Pregnancies after pancreas-kidney transplant occur fairly infrequently. In a recent NTPR report, altogether, only 38 recipients of pancreas-kidney transplants were available for analysis in 2004, with 56 pregnancies and 58 outcomes that included twins and triplets.[4] Table 2 summaries the pregnancy outcomes in these patients.

The mean transplant to conception interval was 3.7 $\pm$ 2.4 years. Maintenance immunosuppression during pregnancy was cyclo-

Table 1.— Post-transplant Pregnancy & Outcome		
	Pregnancy #1	**Pregnancy #2**
Length of pregnancy (weeks)	30	37
Delivery date	July 2002	November 2004
Immunosuppression:		
Cyclosporine	No	Yes
Tacrolimus	Yes	No
Mycophenolate mofetil caps	No	No
Azathioprine	Yes	Yes
Sirolimus	No	No
Prednisone	Yes	Yes
Baby Characteristics:		
Baby's gender	Girl	Boy
Baby's birth weight (lbs, oz)	1 lb., 12.6 oz	5 lbs, 7.7 oz
Baby was healthy	No	Yes
Baby was premature	Yes	No
Baby had complications	Yes (renal insufficiency)	No
Baby was stillborn	No	No
Miscarriage	No	No
Pregnancy Terminated	No	No
Anatomic abnormality	Atrial septal defect	No
Maternal Complications During Pregnancy:		
Diabetes mellitus	No	No
Hypertension	Yes	Yes
Hyperglycemia	No	No
Acute Rejection	No	No

Table 2.— Pregnancy Outcomes in 38 Female Pancreas-Kidney Recipients with 56 Pregnancies Reported to the NTPR	
Maternal Factors	
Transplant to conception interval	3.7 years
Hypertension during pregnancy	75%
Diabetes during pregnancy	2%
Infection during pregnancy	55%
Rejection episode during pregnancy	6%
Pre-eclampsia	34%
Graft loss within 2 years of delivery	16%
Outcomes (n)	**(58, includes twins)**
Therapeutic abortions	5%
Spontaneous abortion	14%
Ectopic	2%
Stillbirth	0%
Livebirths	79%
Livebirths (n)	(46)
Mean gestational age	34 weeks
Premature (< 37 weeks)	78%
Mean birthweight	2,096 gms
Low birthweight (< 2,500 gms)	63%
Cesarean section	57%
Newborn complications	57%
Neonatal deaths, n (%), within 30 days of birth	1 (2%) due to sepsis
Immunosuppression by pregnancy	**n (%)**
Cyclosporine, azathioprine, prednisone	19 (34)
Cyclosporine, prednisone	6 (11)
Neoral, azathioprine, prednisone	13 (23)
Neoral, prednisone	3 (5)
Tacrolimus, azathioprine, prednisone	5 (9)
Tacrolimus, azathioprine	2 (4)
Tacrolimus, prednisone	4 (7)
Tacrolimus, sirolimus	1 (2)
Tacrolimus	1 (2)
Gengraf, azathioprine, prednisone	2 (4)

sporine base in 43 (25 Sandimmune, 16 Neoral, 2 Gengraf) and tacrolimus based in 13. Maternal co-morbid conditions during pregnancy included: hypertension 75%, infections 55%, and pre-eclampsia 34%. Only one recipient reported gestational diabetes; regular insulin coverage was started at 24 weeks but was discontinued postpartum. Rejection occurred during three pregnancies; all three recipients went on to lose their grafts.

There were 46 live-born among the pancreas-kidney transplant recipients; 25 were delivered by cesarean section. One cesarean section was complicated by a tear to the duodenal portion of the pancreas graft that required repair. The mean gestational age of the 46 live-born was 34 $\pm$ 3.1 weeks; 35 (78%) were premature (< 37 weeks). Their mean birth-weight was 2,096 $\pm$ 721 gms and 29 (63%) were low birth-weights (<2,500 gms). By comparison and depending upon immunosuppressive regimen, in kidney-only recipients reported to the registry, the mean gestational age for new-born was 35 to 36 wks, with birth-weights of 2,378 – 2,493 gms.[4] Twenty-six (57%) infants of pancreas-kidney recipients had neonatal complications with one neonatal death from sepsis in a severely premature infant. In a separate study, although the pancreas-kidney offspring have lower mean gestational ages and birth-weights compared to kidney-alone recipients, at a mean follow-up of 5.5 years, all 45 children were reported healthy and developing well.[5]

This case reports the first successful consecutive pregnancies after a pancreas-kidney transplant patient in Hawai'i. The patient was very fortunate to have two healthy children, but not without some complications. Her first pregnancy resulted in a premature infant at 30 weeks, while her second pregnancy was delivered at full-term. As noted above, prematurity occurred in 78% of the NTPR patients. This fact corresponded to the low birth-weight in the first infant of 811 gms. Again, low birth-weights occurred in 63% of the NTPR patients. The patient's first pregnancy required a prolonged stay in the neonatal critical care units, but she was finally discharged home in good condition.

As seen in ther patient, hypertension is very common in pregnant women with a transplant, occurring 75% of the time in registry patients. The patient also developed pre-eclampsia during the first pregnancy which occurred in 34% of the cases in the registry. Cesarean section was employed in both pregnancies. Again, the majority (57%) of registry live-births were delivered that way.

One surprising complication was the oliguric renal insufficiency at birth of the first pregnancy that fortunately did not require dialysis and gradually resolved with time. The hypothesis of the treating physicians was that the tacrolimus may have been a factor. Tacrolimus in high doses can cause renal insufficiency in adult patients after a kidney transplant. After that first experience, it was decided to convert the tacrolimus to cyclosporine for the second pregnancy; the second pregnancy did not develop any renal problems. Azathioprine was used in both pregnancies because the long-term outcome using MMF in pregnancies is not known, and there have been anecdotal reports of birth defects with MMF use. An atrial septal defect was found in the first pregnancy but that has not been associated with immunosuppressive medications in the literature.

Summary

This case reports the first successful consecutive pregnancies after a pancreas-kidney transplant in Hawai'i. Pregnancy can be safe after the first year of a pancreas-kidney transplant, provided that allograft function is stable and that no rejection episode has occurred in the year before conception. All pregnancies in solid-organ transplant recipients should be considered high risk and should be managed by a multidisciplinary team. The expectant mother should be monitored closely (at least every two weeks) by her transplantation physician, and her prenatal care should be preferentially managed by a specialist in high-risk obstetrics. Prematurity and low birth-weights are common. Cesarean deliver is indicated only for obstetrical reasons.

The incidence rates of hypertension and pre-eclampsia can be quite high in these patients and must be managed aggressively. Maintaining appropriate blood levels of immunosuppressive medications may be challenging during pregnancy, but rejection can be avoided and pregnancies do not necessarily harm the transplanted organs. Since immunosuppressive medications must be continued throughout pregnancy, the fetus is inevitably exposed to potential fetotoxic and teratogenic agents throughout development. Prednisone and azathioprine have been used most frequently and appear to be safe. Based on our experience, tacrolimus should be avoided and replaced with cyclosporine for pancreas-kidney patients.

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Bone Marrow Transplant in Hawai'i

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Abstract

Established in 1978, the bone marrow transplant program in Hawai'i includes HLA typing, bone marrow and peripheral stem cell collections, unrelated donor searches and harvests, and transplantations. This retrospective study covers 10 years, from 1999 through June 2009, on 118 adult and 42 pediatric patients. Overall survivals at 1 year for adult transplants were 50% for allogeneic, and 84% for autologous transplants. The 1 year survivals for pediatric transplants were 80% for allogeneic and 71% for autologous transplants. Treatment related mortality has decreased for autologous and allogeneic transplants over the past 10 years.

Introduction

Bone marrow transplantation began with fear and hope. It was the fear of the cancer that created a need for better treatments. It was the hope for a cure that inspired many people to undergo a transplant.

Pioneering work in bone marrow transplantation starting in 1957 by Dr. E. Donnall Thomas immensely contributed to the present knowledge about bone marrow transplantation.[1] In 1990, Dr. Thomas was awarded the Nobel Prize in Medicine for studies in transplantation.[2] In Hawai'i, Dr. Livingston Wong assembled a team dedicated to transplantation and performed the first transplant for a patient with aplastic anemia in 1978.[3] Bone marrow transplants and hematologic stem cell transplantation have provided a second chance to those with cancer over the past 30 years.

The continued success of transplantation depends on the dedicated teamwork of many people: staff, nurses, laboratory technicians, coordinators, and doctors. Bone marrow transplants (BMT) or hematologic stem cell transplants (HSCT) are performed at the Hawai'i Medical Center, which purchased the St. Francis Medical Center in 2007. An inpatient HSCT unit consisting of six beds handles the induction chemotherapy, transplantation, and readmissions. Pediatric transplants are performed at the Kapi'olani Medical Center for Women and Children, where inpatient care is provided through two transplant beds located within a unit focused on oncology care. Outpatient follow-up occurs in a multi-disciplinary team setting, including transplant physician, oncology clinical nurse specialist, nursing staff, physical/occupational therapists, dietician, and a behavioral health specialist.

In addition to transplantation, a Human Leukocyte Antigen (HLA) typing lab provides HLA serological screening and confirmatory DNA typing. The Hawai'i Bone Marrow Donor Registry was established in 1989. The Registry has worked up 2,678 preliminary matches (called confirmatory testing), 284 of which have gone on to donate bone marrow or stem cells. The Registry coordinated 207 bone marrow and 77 stem cell collections from unrelated donors.[4] Since Hawai'i contains a very cosmopolitan and ethnically diverse population of approximately 1 million people, there are many national and international requests for unrelated donor searches looking for multiethnic donors.

This study is a retrospective, single program review of the adult and pediatric HSCT program results from 1999-2009.

Results

During the period from 1999 to June 2009, a total of 160 bone marrow and stem cell transplants were performed. The mean age in the adults was 45.6 years. The mean age was 7.7 years in the pediatrics group. There was 1.36:1 male to female ratio in the adult population compared to a 2:1 male to female ratio for the pediatric cases Ethnicity was not recorded. The overall trends for the total numbers of transplants are shown in Figure 1. Patient characteristics for adult and pediatric transplants are summarized in tables 1 and 2.

The cumulative overall survival rates for both the adult and pediatric transplants are included in tables 3 and 4. Of note, the low survival rates seen in the adult unrelated donor (URD) patients Day +100 and 1-year survival reflect a small number of high-risk leukemia patients with multiple treatment failures.

In the first 100 days, there are many causes for treatment related morbidity and mortality. Complications from graft-versus-host disease, veno-occlusive liver disease, hemorrhagic cystitis, pulmonary failure, diffuse alveolar hemorrhage, renal failure, bacterial or viral or fungal infections, sepsis, hemorrhagic strokes, and congestive heart failure have been reported.[5-8] Over the past 10 years, the treatment related mortality for adult allogeneic transplantations have decreased (see Table 5). This success may be attributable to better conditioning regimens, HLA typing, use of peripheral stem cells transplants, graft-versus-host disease prophylaxis, transfusion support, antibiotics for the myriad of infections, and growing experience with transplantation.[9-11] Although the disease related mortality has decreased over the past 10 years, the malignancies continue to relapse despite hematopoietic stem cell transplantation (see Table 5).

Discussion

Since its inception 30 years ago, the adult and pediatric bone marrow transplant program has served its community in Hawai'i by providing a good therapeutic option with results comparable to mainland centers. We report on the 10-year experience from a single program which includes adult and pediatric patients. Overall survival in the adult and pediatric programs is equal to or better than reported national averages.[12-14] However, there are limited data in our registry about the disease status of the illnesses at time of diagnosis and this precludes a more detailed analysis. Most patients with lymphoma were transplanted when patients had chemosensitive relapsed disease. However, the database did not identify lymphomas transplanted with refractory disease or a second complete remission or the number of treatment regimens to achieve partial remission. Similarly, the acute myeloid leukemias were not documented as primary refractory, first relapse or second complete remission. Finally this is a retrospective review of registry data and the small number of transplants restricts the power of rigorous statistical analysis.

National trends showed an increased use for myeloma, lymphoma, AML, ALL, MDS and older patients.[15-19] Currently, the most common diagnosis for transplantation was myeloma and this was also seen in

Table 1.— Demographics of BMT patients and types of BMT performed		
	Adult	**Pediatric**
Total number	118	42
Range of cases per year	6-20	2-7
Average number of cases	11.8	4.2
Age range	19-69 years	14 months- 19 years
Autologous transplant	68	15
Allogeneic transplant	50	27
Bone Marrow	23	26
Peripheral Blood	94	14
Cord blood	1	2

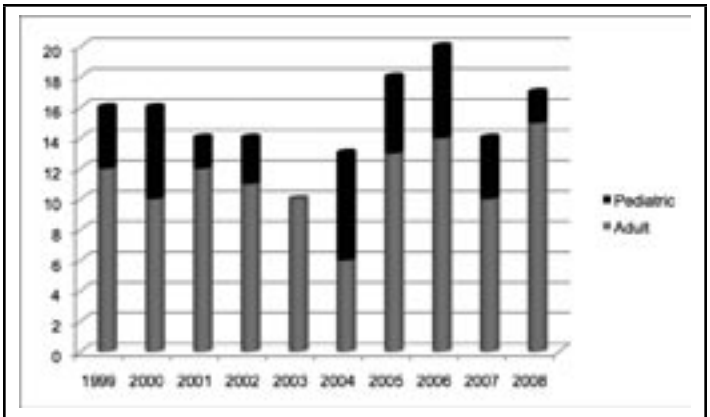

Figure 1.— Total number of adult and pediatric stem cell transplants from 1999-2008

Table 2.— Etiology of diseases for BMT		
Diagnoses	**Adult**	**Pediatric**
NHL	37	3
Myeloma	28	0
AML	21	6
CML	14	1
Hodgkins lymphoma	6	0
ALL	5	10
Breast Cancer	4	0
MDS	2	2
Neuroblastoma	0	12
Congenital neutropenia	0	1
Other	1	7

Table 3.— Adult patient survival after BMT				
Adult Transplantation Overall Survival	**Total n=118**	**Allogeneic n=50**	**Autologous n=68**	**URD n=6**
Day + 100	82%	72%	93%	25%
1 Year	69%	50%	84%	13%

Table 4.— Pediatric patient survival after BMT				
Pediatric Transplantation Overall Survival	**Total n=42**	**Allogeneic n=27**	**Autologous n=15**	**URD n=8**
Day + 100	83%	89%	94%	75%
1 Year	65%	80%	71%	63%

Table 5.— Comparison of mortality in adult BMT patients 1999 vs 2008		
	1999 n=12	**2008 n=15**
Disease related mortality	Allogeneic = 11% Autologous = 33%	Allogeneic = 0% Autologous= 16.6%
Treatment related mortality	Autologous = 33% Allogeneic = 0%	Allogeneic = 13.3% Allogeneic = 0%

Hawai'i; multiple myeloma has been the most common diagnosis for adult autologous HSCT in Hawai'i for the last three years.[20,21] There was a significant decrease in use of transplants for CML since 2000 with new tyrosine kinase inhibitors such as imatinib.[22,23] These national trends were also noted in Hawai'i. In addition, there were an increased number of autologous HSCT, decreased number of allogeneic HSCT, and an increased use of peripheral stem cells rather than bone marrow for stem cell collection.[24,25] The small number of Unrelated Donor (URD) transplants over six years in Hawai'i reflects the small state population.

In the 30 years since the start of transplantation in Hawai'i, there has been a sea change of improvements. There are more effective medications for graft-versus-host disease, infections, and growth factor support for hematopoiesis. Improved induction therapies have decreased the Day 100 treatment-related mortality from 40% to less than 5% in adults. The increasing use of peripheral stem cells has diminished the time to engraftment, but has increased the rate of acute graft-versus-host disease due to the total dose of T-cells reinfused.

In comparing the adult and pediatric results, there are significant differences. Neuroblastomas are much more common in the pediatrics, than in adult populations. In contrast, myelomas, lymphomas, and breast cancers are much more common in adults, than in children. Thus, the age-related rates of diagnosis reflect the frequency in the illnesses.

In Hawai'i, transplantation has been limited by the small population. In addition, due to referral patterns and insurance issues, many of those in Hawai'i that would be considered for BMT have been referred to mainland centers. Thus, the number of patients eligible for transplantation will continue to remain small. In spite of the smaller volume of our center, our 10-year data demonstrates good results for autologous and allogeneic transplantation.

Summary

Currently, stem cell transplantation offers a light of hope in the darkness of fear. Through the efforts of many people, bone marrow and stem cell transplantation has been a success in Hawai'i. For many adults and children, transplantation represents a second chance in life after a disease with otherwise dismal prognosis. The adult and pediatric transplant programs in Hawai'i have persisted despite many barriers and challenges. Future progress will require

creativity, innovation, dedication, hard work, and compassion. In the words of Dr. Livingston Wong, "The future is for the young at heart and strong of will. Those who can take medicine to next level will be the leaders."

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(Dr. Livingston Wong, one of Hawaii's pioneering transplant surgeons, left, extracts bone marrow from a donor.)

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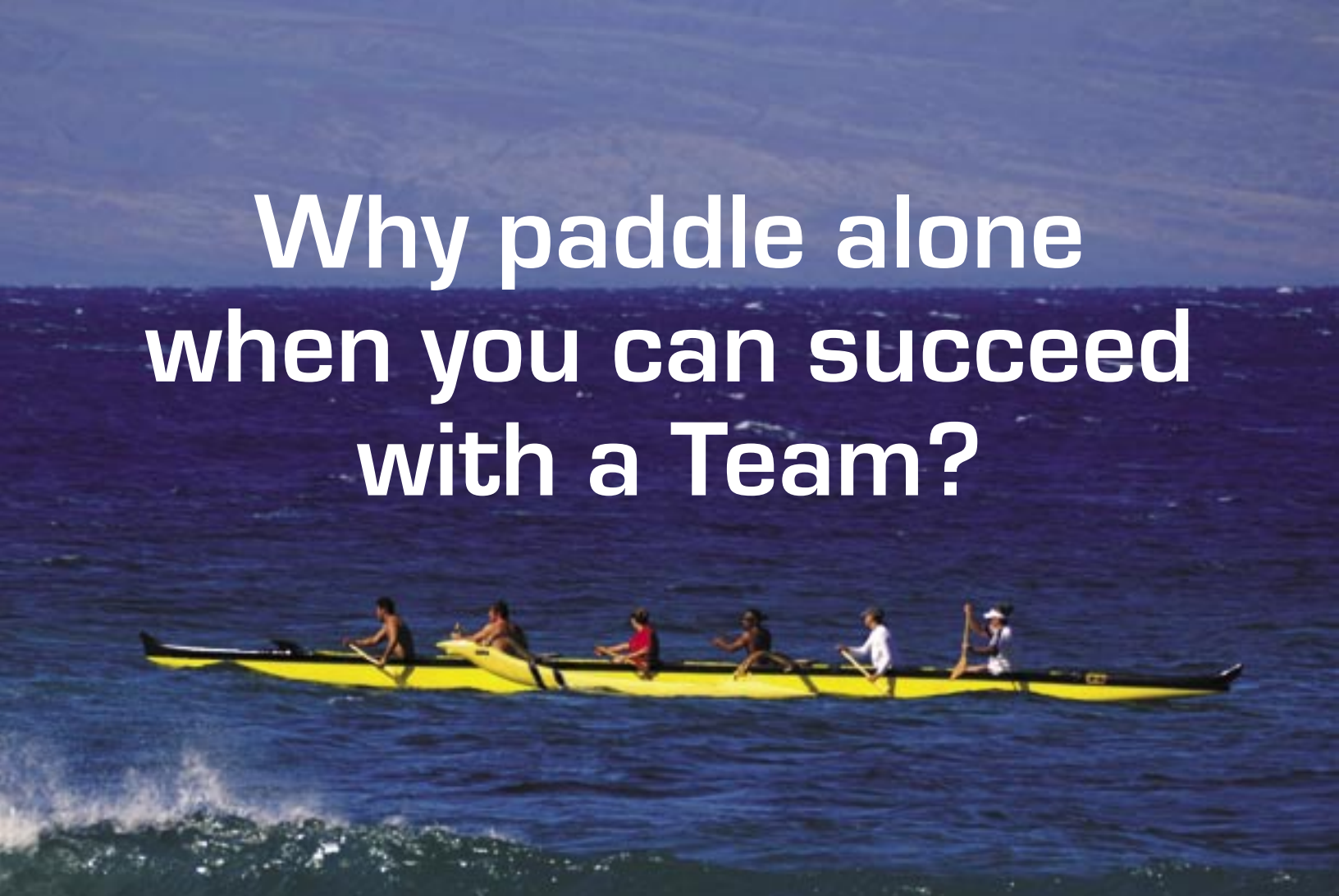

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