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The University of Western Ontario Medical Journal
Volume 82, Issue 1, Spring 2013

GENITOURINARY

UWOMJ

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COVER ART: Arvand Barghi

FRONT: In my illustration I tried to portray the vibrant and flowing nature of the kidney

Sailing ahead

Joyce T.W. Cheung (Meds 2013)

As the academic year comes to a close for many of us, we are anticipating a fresh and exciting chapter of our lives. I would like to congratulate the 2013 class and use this platform to thank them for their contributions to the UWOMJ throughout the years. Personally, it has been a pleasure to be a part of the UWOMJ team and the quality of the contributions has never ceased to amaze me.

Our latest issue features the incredible genitourinary system and developments in this field. It is difficult to think about the genitourinary system and not have your curiosity piqued by the fascinating topic of organ transplantation. Within the last century, the concept of allograft transplantation has evolved from a procedure that was doomed to eventually fail to a common reality, due to advances in surgical technique and immunosuppressive medication. Our feature article by Alex Jiang outlines the latest in double-organ transplantation of the pancreas-kidney, and its therapeutic role for those suffering from diabetes and end-stage renal disease. Technological advancements have allowed for less invasive methods of performing surgery, and Laura Callan and Nancy Chen outline the field of surgical robotics and give us the latest on research initiated here at Western University.

Behind the glamorous façade, the topic of organ transplantation is as complex as they come. Controversial topics range from ethical problems surrounding candidate selection, to the surgical skill required in performing the transplantation, to medical care afterwards to reduce the risk of organ rejection. To start, organs are still an extremely scarce resource, so how do we decide on who gets to undergo this life-changing procedure? Kyle Luong writes about the process of kidney allocation and the complexities of choosing an appropriate candidate. The unpredictable nature of having a suitable donor organ has led to the business of transplant tourism, which is introduced to us in this issue by Saad Ahmed. For those that are left on the waiting list, long-term hemodialysis is a life-sustaining treatment. Justine Denomme and Wendy Cui outline the barriers to accessing hemodialysis, from its introduction to the current state of the system. Our featured clinician, Dr. Faisal Rehman, is no stranger to the world of renal disease and its treatment. In our interview with Dr. Rehman, he speaks about his vision for the future of renal medicine and recalls a case that reminded him that despite our advances, we still have so much more to learn.

We take a step back from the complex world of transplantation and march into the front lines of medicine. In the world of primary care medicine, preventative health and prostate cancer screening has become a controversial issue over the years. Our editors update us on the topics of the role of prostate-specific antigen and the digital rectal examination in prostate cancer screening. From the simple urinary tract infection to life-threatening urosepsis, Anthony Chow and Elaine Tang teach us how to approach fever and incontinence in the emergency department.

All in all, we have prepared an exciting issue that covers complex tertiary care topics and also important primary care and preventative health issues related to genitourinary medicine. Congratulations to our contributors and reviewers for a fantastic year, and a big thank you to our readers for your continued support!

Simultaneous pancreas-kidney transplantation: the role in the treatment of type 1 diabetes and end-stage renal disease

Alex Jiang (Meds 2015), BHSc

Faculty Reviewer: Dr. Patrick Luke, MD, FRCSC (Division of Urology, Department of Surgery)

BACKGROUND

Type 1 diabetes mellitus (DM) is one of the most common chronic diseases of childhood caused by insulin deficiency secondary to autoimmune destruction of pancreatic beta-cells. The condition affects approximately 1.4 million individuals in United States with an annual incidence of 17 cases per 100000 children.[1] Unmanaged, it can lead to severe long-term complications. These include microvascular events, such as retinopathy, neuropathy, and nephropathy, and macrovascular diseases involving cerebrovascular, coronary or peripheral vascular systems.[2,3] These complications are largely attributed to hyperglycemia resulting from poor insulin secretion. Consequently, the mortality rate for type 1 DM is high - 13% after 20 years of disease.[4]

One of the most signification complications of type 1 DM is end-stage renal disease (ESRD).[5] It initially manifests as microalbuminuria with subsequent progression to proteinuria. Without intervention, 80% of these cases lead to nephropathy and ultimately, ESRD (glomerular filtration rate <15 mL/min/1.73 m^2). Eligible patients with ESRD require dialysis or renal transplantation for long-term management.[6]

The Diabetes Control and Complication Trial (DCCT) demonstrated that tight glycemic control, achieved through intensive insulin therapy, slows the progression and reduces the risk of developing micro- and macro-vascular complications.[7] Despite use of insulin pumps and intensive insulin therapy, no exogenous delivery of insulin has been able to sustain normoglycemia as effectively as a functional pancreas. As such, allogeneic pancreas transplantation was developed to achieve normoglycemia and insulin independence. The combination of pancreas and kidney transplantation can render a patient free of both insulin and dialysis with prevention of further diabetic complications, and occasional reversal of established disease.[8]

PANCREAS TRANSPLANTATION HISTORY

The first pancreas transplantation (PT) was performed in 1966 by William Kelly and Richard Lillehei at the University of Minnesota in conjunction with a kidney transplant to treat a diabetic uremic patient.[9] Early procedures were associated with significant morbidity and mortality and performed in low numbers in very select patients. With the advent of cyclosporine and improvements in surgical techniques, one year graft survival rates exceeded 70% in 1980s.[10] To date, more than 32000 cases have been performed worldwide with ever improving outcomes.[11]

Currently, there are three methods of solid organ pancreas transplantation. The majority (83%) of procedures are performed in the context of simultaneous pancreas-kidney (SPK) transplantation where the pancreas is transplanted at the same time as the kidney. The second method is pancreas after kidney (PAK) transplantation (12%) where a pancreas is transplanted to a patient who previously received kidney transplantation. The third method is pancreas transplant alone (PTA) (5%), which involves transplantation of a solitary pancreas to a diabetic patient with normal renal function. This is performed to counteract life-threatening hypoglycemic unawareness or rapidly progressive diabetic complications refractory to intensive insulin therapy.[12]

SELECTION PROCESS

The SPK procedure is usually reserved for a patient with type 1 DM as confirmed by low or absent level of C-peptide.[13] Candidates may also have significant nephropathy or ESRD, along with complications such as hypoglycemic unawareness, recurrent hospitalization from diabetic ketoacidosis, progressive retinopathy, enteropathy and neuropathy.[14]

SURGICAL PROCEDURE

The techniques used for SPK transplantation are diverse and institution-dependent. Most transplant centers use the intraperitoneal approach for graft placement. The pancreas is transplanted to a heterotopic location, usually the right iliac fossa, while the kidney is transplanted to the contralateral iliac fossa. This approach results in fewer peripancreatic fluid collections and wound complications. An alternative approach involves extraperitoneal and ipsilateral placement of both grafts.[15]

Arterial anastomosis may be performed by conjoining the donor superior mesenteric artery and splenic artery to a Y graft of the recipient external or common iliac artery. The donor portal vein is anastomosed to the external iliac vein if systemic drainage is provided. An alternative approach is anastomosis of donor portal vein to superior mesenteric vein if portal venous drainage is available.[16] Although this was performed to reduce lipid dysregulation and rejection rates, contemporary studies have shown very little differences in overall long-term outcomes between systemic and portal drainages.[17]

OUTCOMES

Survival

It is believed that the SPK procedure prolongs patient survival beyond the survival advantage associated with renal transplantation alone. The 5- and 10-year patient survival rates for SPK transplantation is 87% and 70%, respectively.[18] This is significantly better than the survival rates for type 1 diabetics receiving maintenance dialysis and who are on transplant waiting list.[19] However, due to inherent biases in listing candidates for transplants, and the differences in donor age between SPK and solitary kidney (SK) transplant cohorts, the true survival benefit conferred by the pancreas is unknown.

Graft survival rates are excellent. The pancreatic allograft survival rate is 86% at one year and 53 % at 10 years while kidney survival rate is >95% at one year and 60% at 10 years.[18,20] The lower one year graft survival rates for the pancreas are secondary to early transplant compli-

cations, including thrombosis, pancreatic fistula, and infection.[18,20]

Quality of Life

Pancreas transplantation can improve quality of life (QOL) by eliminating diabetes associated complications, including hypo/hyperglycemia, metabolic derangements, insulin dependence, glucose monitoring and dietary restrictions.[21] Smith et al. compared pre- and post-transplant QOL and found significant improvement following SPK transplantation.[22] SF-36 Mental Component Summary scores were significantly higher 2 years post-transplant compared to pre-transplant (51.8 vs. 46.8). Similar results were obtained from the Physical Component Summary (PCS) score (48.1 vs. 40.6).[22]

Glycemic Control

The vast majority of patients achieve complete insulin independence over the short and long-term following solid-organ pancreas transplant. In fact, glycemic control is far superior to that achieved by insulin pump or islet-cell transplants.[23] Mora et al. demonstrated that recipients achieved long-term normoglycemic state following SPK transplant.[24] During the 15 year follow-up, HbA1c level remained within normal range with no significant difference between the first and the last year of follow-up (4.68% vs. 4.76%, $p>0.05$).[24] Fasting glucose level also remained stable during the same period (3.94 vs. 4.38 mmol/l, $p>0.05$).[24] However, oral glucose tolerance test (OGTT) demonstrated decreased pancreatic response, indicating certain deterioration in the functional capability of the allograft over the long-term.[24] Whether this is the effect of immunosuppressive medications (i.e. tacrolimus, sirolimus and prednisone) on islet-cell function, insulin resistance, immune-related chronic changes, or a combination thereof, is unknown.

Vascular

The pancreas transplant does not reverse established macrovascular disease in recipients. Instead, it is believed to slow down the progression of disease in this high-risk population. Nevertheless, five years after transplantation, the prevalence of cerebrovascular disease (CVD), coronary heart disease (CHD) and peripheral vascular disease (PVD) is still 33%, 41% and 41%, respectively. Ten years after transplantations, the risk increased only slightly to 41%, 50% and 50 %, respectively.[25] Using peripheral thermography studies, it is believed that microvascular perfusion is improved post-pancreas transplant as a result of better glycemic control.[26]

Neuropathy

Previous studies demonstrated a benefit of SPK transplant for diabetic polyneuropathy. Kenedy et al. analyzed the effect of pancreas transplantation on peripheral motor, sensory and autonomic nerve function based on indexes of nerve conduction velocity and muscle action potential.[27] After 12 months of follow-up, they found a significant improvement in motor and sensory indices. This is supported by Martinenghi et al., which demonstrated that a sustained normoglycemic state can ameliorate nerve function even if polyneuropathy is advanced.[28]

Table 1: Selection Criteria for SPK Transplantation[13]

Confirmed diabetic nephropathy on insulin
Presence of other secondary diabetic complications
Ability to endure surgery and immunosuppression
History of compliance to medical recommendations and therapies
Understanding of potential morbidity and mortality
Creatinine clearance <15 ml/min or on dialysis

Nephropathy

Most patients with type 1 DM and ESRD receive SPK to improve their renal function. Fioretto et al. reported that 10 years of sustained normoglycemia post-transplant reversed features of diabetic nephropathy.[29] It significantly improved glomerular and tubular lesions, and reduced the thickness of glomerular basement membrane and mesangial matrix. A decrease in urinary albumin excretion rate was also observed (20 mg/day vs. 103 mg/day) highlighting improvement in renal function. However, improvements in diabetic nephropathy post-transplant need to be balanced with nephrotoxicity incurred by the use of immunosuppressive agents such as tacrolimus and cyclosporine.[30]

Retinopathy

Diabetic retinopathy (DR) is the most common microvascular complication of diabetes. Several studies have reported conflicting results about the effects of SPK on retinopathy. However, most recent studies indicate that SPK, with subsequent normalization of blood glucose level, can improve or normalize retinal lesions.[31] Following SPK transplantation, 14% of non-blind eyes showed improvement, 76% remained stable and only 10% progressed further.[32] A separate study reported an improvement in post-transplant visual acuity in 32% of the eyes and frequency/severity of vitreous hemorrhages in 46% of eyes.[31] It may take up to 4 years before noticeable functional improvement in retinopathy and acuity may be observed. Pancreas transplantation, however, cannot reverse established visual loss.

CONCLUSION

SPK transplantation is the most effective treatment for patients with type 1 DM and ESRD. It addresses renal failure and provides physiological means of attaining stable insulin secretion. Although it involves major surgery and is not without risks, it nonetheless increases patient survival, enhances QOL and prevents progression of diabetic complications. As such, they should be considered in all eligible patients.

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Pathogenic mechanisms and direction of empirical studies: a retrospective on membranoproliferative glomerulonephritis

Alexander Pazionis (Meds 2015) and Denise Darmawikarta (Meds 2016)

Faculty reviewer: Dr. Faisal Rehman, MD, FRCPC, M.Ed (Department of Medicine, Division of Nephrology)

Membranoproliferative glomerulonephritis (MPGN) is an immune-mediated disease process, underlying 10%-20% of nephrotic syndrome cases in children and young adults.[1] The Type I subtype (Classical MPGN) is the most common Hepatitis C Virus (HCV)-associated nephropathy.[2] Still, though all MPGN subtypes (I,II,III) can slowly progress to end-stage renal disease (ERDS),[3] the condition is uncommon enough to account for just 2.8% and 3.3% of all cases in pediatric dialysis patients and pediatric renal transplant recipients, respectively.[4] This may explain, in part, why studies on the efficacies of various immunosuppressive agents in this condition are, on the whole, relatively limited.

Nevertheless, the general findings (with exceptions) appear to indicate these agents are either ineffective or minimally effective in MPGN (depending on the subtype). In the current model of evidence-based medicine (EBM), it is understandable that much of clinical practice and research be guided by empirical findings. Nonetheless, when examining the theoretical pathogenesis of MPGN along with what is known of the mechanisms of action of these agents, it retrospectively becomes clear that some of these agents were unlikely to be effective in the first place. This is not to say that theoretical understanding should be trusted without empirical verification. However, in the same way that a clinician should consider what is known about an individual patient and order tests accordingly, it behooves the investigator to consider what is known about a condition before conducting an empirical study.

In this review, we discuss the underlying pathogenenic mechanisms of MPGN and review currently available treatment. We focus on idiopathic MPGN, as most cases of MPGN in adults have secondary causes (e.g. cancer, hepatitis C) and treatment would accordingly target those underlying conditions.

PATHOGENIC MECHANISMS

The complement cascade consists of a series of proteolytic steps catalyzed by the products of previous steps in the series.[8] Figure 1 is a diagrammatic representation of the complement cascade, which can be activated via more than one pathway; the two most relevant to the discussion being the so-called 'classical' and 'alternative' pathways.

The classical pathway is part of the arsenal of the adaptive immune system's humoral arm.[8] The alternative pathway, on the other hand, is a part of non-specific or 'innate' immunity, and does not require antibodies, like the classical pathway does.[8] However, after the cleavage of C5 to C5a and C5b, classical and alternative pathways converge to a common molecular sequence.[8] It is at this stage, the so-called 'terminal' pathway that over-activation seems most highly associated with MPGN III.[3, 9, 10] With this in mind, we may classify the subtypes of MPGN as follows:

Type I – Evidence of activation of the classical and alternative complement pathways, exhibiting on immunohistochemistry glomerular deposits of immunoglobulin (indicating immune complex deposition as a contributor to the disease process), as well as components unique to the classical complement cascade (C1q, C4) in addition to those common to both the classical and alternative pathways (C3).[1]

Type II – Also known as 'Dense Deposit Disease,' with conspicuous absence of components unique to the classical compliment cascade (C1q, C4) vis-à-vis absence of immunoglobulin deposition, while still maintaining evidence of C3 deposition in the kidney(s).[1] The implication is a 'pure' alternative pathway component and a theoretical absence of an adaptive immunity contribution.

Type III – Less easily classified and arguably the rarest of the three commonly acknowledged subtypes. It is often considered a variation of Type I. It displays evidence of possible immune complex deposition as a mediator of glomerular damage via the observation of immunoglobulins on immunohistochemistry, but, as mentioned previously, is also highly associated with over activation of the terminal pathway of the complement cascade.

While the pathogenesis of MPGN is now becoming clearer, it is interesting to realize that currently employed therapeutic agents do not necessarily target components of the disease mechanisms.

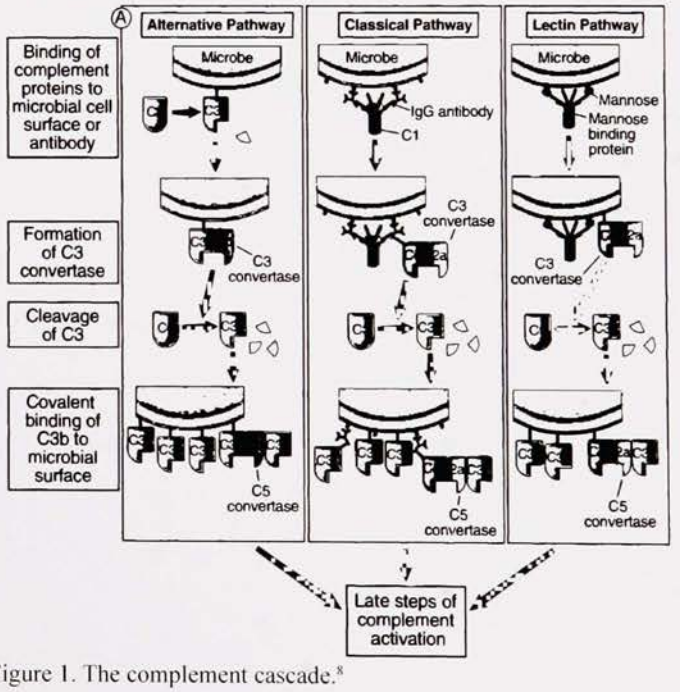

Figure 1. The complement cascade.[8]

CORTICOSTEROIDS

An important study to consider in detail is a report of the International Study of Kidney Disease in Children.[11] This study showed a statistically significant decrease in treatment failure for children with MPGN I and III, meeting their inclusion criteria when treated with prednisone rather than placebo ($p = 0.028$). However, results were not statistically significant for children with MPGN II included in the study, though it was underpowered in this regard. This was corroborated by Donadio and Offord,[12] whose study also failed to show benefit in adult MPGN II patients comparing prednisone to placebo. Finally, though not quite reaching statistical significance ($p = 0.07$), there was a trend toward stable, improved renal function considering all participants with MPGN I, II and III at 130 months of follow-up.[11] A weakness of this study is that it did not differentiate between MPGN I and MPGN III under the assumption that MPGN III was a subcategory of MPGN I. Potential differences between these two groups were evaluated in a retrospective study by Braun et. al [13] that showed statistically significant differences between a number of characteristics between MPGN I and MPGN III patients treated with prednisone at 3 years of follow up. Patients with MPGN I, compared with those having MPGN III, were found to have more stable GFR's, lower rates of persistent hypocomplimentemia (C3), and lower rates of persistent hematuria and proteinuria, to name a few.

Thus, with what evidence there is, a possible theoretical simplification is as follows with respect to the effectiveness of steroids in MPGN:

MPGN I – Effective

MPGN III – Less Effective

MPGN II – Not Effective

The effects of steroids are so categorically broad that any explanation on a mechanistic basis of these categories would amount to speculation. More simply put, it is difficult to identify differences in similar disease entities based on responses to a drug with broad effects. Other agents with greater specificity allow us to better distinguish such differences on the basis of theoretical knowledge. This is illustrated next, by the admittedly limited number of studies performed on calcineurin inhibitors.

CALCINEURIN INHIBITORS

Calcineurin mediates the activation of nuclear factor of activated t-cells (NFAT), a transcription factor encoding a number of genes including IL-2.[8] IL-2 is necessary for T-cell proliferation.[14] Other genes, such as CD40L and others required for T-cells to be able to activate B-cells are also produced. Blocking calcineurin, therefore, is expected to have a number of effects on the adaptive immune system including decreased antibody production and decreased T-cell inflammatory mediator release.

The possibility of using calcineurin inhibitors is best illustrated in two studies. The first, by Bagheri et. al. studied 18 patients with idiopathic MPGN (IMPGN)[15]. They showed that partial or complete remission of proteinuria was achieved in 94% ($p<0.01$) of patients, and that at an average follow-up of 108 weeks, just one of those showed remission once treatment was discontinued[15] .Another study, by Singh et. al. similarly showed statistically significant reductions in proteinuria in 8 patients with MPGN treated with cyclosporine[16].However, both of these studies failed to distinguish between different subtypes of MPGN. Bagheri et al. made no mention at all of different subtypes, and though Singh et al. disclosed that 5 of the MPGN patients were Type I and 3 were Type II, the data for all these patients were ultimately combined. The pathogenesis of MPGN I is directly linked to the classical pathway of compliment activation, which constitutes part of adaptive immunity and therefore is, in theory, potentially susceptible to inhibition by calcineurin inhibitors. This cannot be stated with certainty based on the studies discussed as they did not dissociate the effects of calcineurin inhibitors on type I vs. type II. MPGN II, on the other hand, is linked to innate immunity, and though there have been incidental case reports of MPGN II patients responding to cyclosporine[14], long-term follow-up studies of small numbers of patients show that calcineurin inhibitors have no impact on renal survival in MPGN II patients[17]. Long-term renal survival in MPGN I patients treated with cyclosporine should be further investigated.

CONCLUSION/FUTURE DIRECTION

While some evidence exists that suggests a role for other treatments, such as acetylsalicylic acid, dipyridamole, cyclophosphamide and Coumadin (warfarin), in MPGN, it is unfortunately of poor quality[18]. Randomized controlled trials should be conducted to study these various treatment options for MPGN. Given the general ineffectiveness of current MPGN treatment, it is imperative that future investigations on potential therapeutic agents be conducted on the basis of known pathogenic mechanisms.

A promising treatment option for MPGN that has been elucidated by case reports 5-7 is Eculizumab. Eculizumab is a monoclonal antibody for C5, a member of the complement cascade that forms part of the MAC. Given the pathogenesis of MPGN, the use of Eculizumab makes intuitive sense and thus it is unfortunate that little is yet known about their effectiveness in the treatment of MPGN. Insofar as C5 is involved in both the classical and alternative pathways of complement activation, all three subtypes of MPGN (which, somewhat simplified, may be characterized by differential ratios of classical:alternative pathway activation), could theoretically be treated with this medication. Future studies should therefore investigate the potential for Eculizumab in treating MPGN, insofar as potentially, all three subtypes of MPGN could be treated with this agent.

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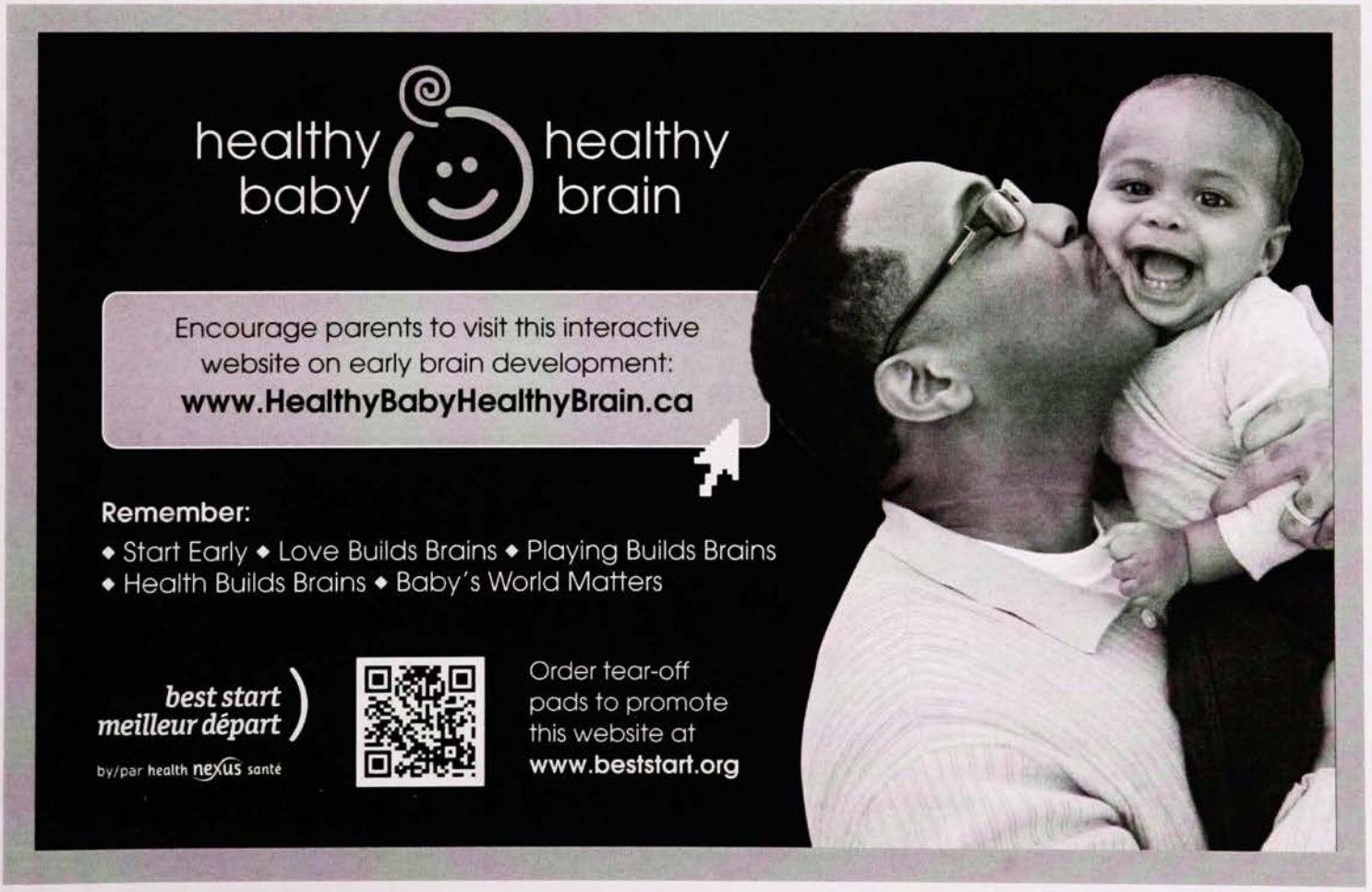

Digital rectal examination in prostate cancer screening

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INTRODUCTION

Digital rectal examination (DRE) may be performed in order to identify rectal disease, prostate cancer, examine anal sphincter tone, or to examine female gynecological structures. Rectal examination has been described by conflicting opinions as both a cause of "more harm than good" and conversely as a "crucial part of the examination [of a patient]".[1, 2] Despite its many diagnostic applications, the test is also uncomfortable for some patients, doctors, and medical students. This article will focus on the characteristics of the test in prostate cancer screening, and how the challenges of patient resistance and medical student education can be addressed.

ROLE OF DRE IN PROSTATE CANCER SCREENING

What lies at the center of the DRE debate is its utility for identifying and diagnosing different diseases. One application for DRE is for the detection of prostate cancer which is the most common cancer in men other non-melanoma skin cancers. It was diagnosed in 26,500 Canadians in 2012, and resulted in 4000 deaths.[3] However the disease is often indolent, and while one in seven men are diagnosed, only one in 27 men die from the disease.[4] The value of DRE can come into question because studies conflict as to whether screening for prostate cancer can lower morbidity.[4] Nonetheless, because of the frequency of the disease and the possibility detecting the disease when it is curable many patients and physicians choose to screen.

The DRE is an inexpensive test that involves assessment of prostate size, consistency, mobility, and irregularities in shape. However the size alone is not a useful predictor of prostate cancer risk and there is low correlation between transrectal ultrasonography (TRUS) measured prostate volume and DRE estimated volume.[5,6] Additionally, while carcinomas are felts as hard irregular nodules similar indurations may also be caused by benign prostatic hypertrophy (BPH) or calculi. This means an examiner must order further tests when any induration is felt, and repeat the test regularly to detect for any changes or progression.[5, 4] The exam also requires technical skill. Not all examiners can palpate the entire posterior surface of the prostate. The ability of an examiner to reach and examine the apex of the prostate, half of the prostate, three quarters of it, and the entire prostate in a recent study was 93.7%, 66.3%, 23.2% and 3.2% for these respective components of the prostate gland.[7] Evidence for the importance of technical skill in DRE also comes from studies of inter-examiner variation. One study compared consultant and resident urologists who performed DREs to determine if prostates were suspicious for cancer. The overall agreement was expressed with a kappa statistic of 0.22, which suggests only fair agreement between examiners. However, while the kappa statistic among residents was 0.25; among consultants it was 0.63 which suggests a substantial level of agreement.[8] Further research has shown that more experienced urologists tend to assess the size of a prostate more accurately.[9] These findings support the idea that technical skill is important to successfully performing DREs. One means to address this is through improved education of medical trainees, a topic addressed later in this article.

When DRE is used to screen for prostate cancer in men over 50 years of age, the cancer detection rate is 3.2% with a positive predictive value of 21%. The sensitivity and specificity of DRE are 21% and 86% respectively.[10] It is also recommended that DRE is performed in conjunction with prostate specific antigen (PSA) in prostate cancer screening because this improves the overall sensitivity. Whereas the prostate cancer detection rate was 3.2% for digital rectal examination, it was 4.6% for PSA and 5.8% for the 2 methods combined.[11] Of note is that the detection rates of the two tests only partially overlap, and together the two tests detect more cases of prostate cancer.

In conclusion, because the disease is relatively indolent, it is recommended that an informed decision is made by patients whether or not to screen for prostate cancer. Because the test is technically difficult to perform, steps should be taken to improve the education of medical trainees. If screening is to be performed, then regular DRE is recommended to be used conjunction with PSA testing to increases the rate of cancer detection.

PATIENT BARRIERS

Some patient barriers to the acceptance of DREs include discomfort, embarrassment and men associating the exam with homosexuality. Furthermore some men are worried about feeling stimulated and having an unwanted and uncontrolled physical response during a DRE. Men may not seek medical attention that includes DRE until they're no longer able to cope with symptoms; this could be due to both fear of the procedure or fear of discovering illness. One way to improve patient acceptance of DRE is to improve patient education. Ample information on the process and reason for performing the procedure should be provided for patients. To be included in the conversation could be discussion about past experiences with DRE, whether positive or negative. Positioning can also be chosen to reduce patient embarrassment during the procedure. The left lateral position has been show to be the least embarrassing without compromising the results of the test.[12] Furthermore, many patients view colonoscopy drastically differently than DRE. The reason is that colonoscopy is often perceived as more technological and hence perceived as more scientific. Therefore extra care should be taken by physicians to maintain a professional environment during DRE. Language used should be chosen carefully. For example, phrases like 'examine' the prostate rather than 'feel' the prostate make the process sound more clinical and scientific, hence more accepted by patients who are wary of the procedure.[13]

TEACHING OF THE DRE

One factor limiting the usefulness of DRE is inter-examiner variability, which results in inconsistent exam findings. This has promoted studies that examine how the digital rectal exam is taught to medical students and residents. Teaching during medical school has a huge bearing on a physician's future skill in performing DRE, yet several aspects limit what students learn. DRE is often learned through textbook readings and facilitator demonstrations. The three dimensional nature of the prostate is difficult to convey in textbooks. In demonstrations, it is challenging to teach the subtleties of palpation because DRE is a very internal procedure.[14]

One attempt to solve this problem uses rectal simulators which are currently being developed to teach the DRE. A mannequin modeling the rectum and prostate is attached to electronic sensors, so that when an examiner palpates the rectum sensors analyze the pressure and location of palpation for instructors to assess and give feedback. Beyond use as a teaching tool, this simulator can also detect differences in performance between examiners and so attempts to quantify inter-examiner variability in DRE.

University of California Medical School developed a DRE teaching model that include didactic lectures, practical learning by performing the procedure on a standardized patient, and small group sessions led by faculty members. In a study conducted by Kaplan et. al, students' comfort level in terms of performing DRE were comparing between group of students that received DRE training from the new teaching model and students that didn't receive formal training in performing DRE. Students who had received the teaching model were more comfortable performing DREs. Examiner comfort and confidence level is crucial to patient comfort and confidence; hence this model of learning through three modalities should be given consideration for more widespread use in the teaching of medical students.[15]

CONCLUSION

Despite differences in prostate cancer screening guidelines between various countries, the majority of countries recommend a combination approach of serum PSA with DRE.[16] Therefore DRE is still an important part of undergraduate and postgraduate medical curricula.

Things to keep in mind:

- Reassure your patient: explain to them why you're doing this exam and what to expect during the exam.
- Use medical terms to describe procedure: examine, palpate, drape, examination table etc.
- Ask the patient if they have ever had a bad experience during a DRE.
- Position choice: left lateral position is perceived by patients to be least embarrassing, while achieving similar results as other positions.[16]

There are limitations to use of DRE in prostate cancer screening. However as a procedure that is low risk, fast and office setting procedure when used in combination with PSA increase cancer detection comparing to PSA alone, there is still a place for DRE in medicine and prostate cancer screening today. There is inter-examiner variability meaning that experience level has an impact on efficacy of this test. Therefore DRE should to be more rigorously taught to new generations of physicians and care should be taking regarding how DRE is taught. Modifications should be made to the teaching of this procedure in medical schools. Traditional learning from texts and demonstrations should be enhanced by the incorporation of modern technology like DRE simulators and more comprehensive teaching models to educate future physicians.

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A short primer on transplant tourism

Saad Ahmed (Meds 2016)

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Male, 45 years old, presenting with severe sepsis – rushed in straight from the airport. On further investigation the patient also has an inflamed incision lateral to their upper right abdominal quadrant that seems infected. The family seems tight-lipped about the details of the trip, but on pressing they mentioned a kidney transplant done abroad as the reason.

What do you do in this situation?

INTERNATIONALLY:

In 2008 delegates from all around the world drafted the Istanbul Declaration. It explicitly stated that organ trafficking and commercialism exploits the poor and should be completely banned.[1] Whereas organ trafficking is done with coercion and usually violence, even organ commercialism involves a certain amount of monetary coercion, especially since there are power asymmetries between someone in a developed country and a desperately poor person in a developing country.[1] Those who are forced to sell their kidneys as a result of financial hardships frequently report that they are left frail and sick, with the money disappearing in no time.[2] Secondly, multiple studies from Canada, the US, and Australia have shown that the health outcomes of transplants tourists are significantly worse than patients who received their transplants domestically and legitimately.

The policy makers at the Istanbul Declaration recognized that organ trafficking and commercialism is ultimately driven by demand from people in developed countries who are suffering on organ recipient waitlists. To this end, they reinforced the importance of policies that increase domestic organ donation rates,[1] some of which have been adopted in Canada. An example of these policies being put into practice is the Living Donor Paired Exchange (LDPE) Registry, a national registry for patients suffering from chronic kidney disease, and the Living Organ Donor Reimbursement Program (LODRP), which has been adopted in at least 5 provinces. The LODRP reimburses organ donors for various expenses and time lost throughout the process of donation and recovery. The LDPE matches transplant patients who have incompatible living donors with each other – the idea being that one patient's incompatible donor may be compatible with another patient, whose living donor may be compatible with the former patient. It has been shown to increase organ donations by up to 10%.[3]

The Declaration has had significant influence globally – especially in countries formerly considered to be hotbeds of organ trafficking and commercialism, such as China, Pakistan and the Philippines. Legislation is now in place to prohibit the practice.[4] Countries are also working together to apprehend and charge those who continue to participate in organ trafficking. For instance, European and Canadian authorities in Kosovo recently dismantled an infamous organ trafficking ring spread out across three continents; and a criminal trial has begun to sentence the traffickers.[2]

DOMESTICALLY:

In Canada, the Canadian Society of Transplantation and the Canadian Society of Nephrology jointly released a policy statement on organ trafficking and transplant tourism. In their preamble, they affirmed the principles of the Istanbul Declaration[5] and a physician's duty to never deny care to a patient. The main crux of the policy statement is focused on preventing people from undergoing transplant tourism in the first place.[4] The myriad problems and complications of transplant tourism should be coherently communicated to patients – such as the difficulty in receiving insurance coverage for long-term anti-rejection medications due to the lack of documentation and unethical nature of the transplant.[4] To this end, the Kidney Foundation of Canada released a set of pamphlets that warns people about the possible consequences of transplant tourism (see http://www.kidney.ca/document.doc?id=1239).

The data from a single centre study which looked at 93 transplant tourists from British Columbia, affirms the need for thorough and proper pre-transplant counseling.[6] The study found that 30% of the respondents had never been referred for a transplant consult, and had thus preemptively undergone a kidney transplant. Another 33% of the transplant tourists in the study had completed a transplant consult, and after being waitlisted for a transplant sought a commercial transplant. This speaks to a need for a multi-faceted policy. If 30% of transplant tourists are pre-emptively receiving transplants without an actual referral after the development of end-stage renal disease, it speaks to a need for public campaigns discouraging transplant tourism, as well as a need to educate patients before the development of end-stage renal disease. Secondly, other patients received a referral, but failed to follow up and were lost to the system – hence the study mentions that patients must be tracked better. Furthermore, considering that the vast majority of transplant tourists were ethnic minorities,[5] the study argued that outreach efforts must be made to members of these communities to discourage transplant tourism. And for the 33% of patients who had gone abroad for a transplant after being put on a waitlist, the study advocated for policies such as the Paired Living Donor Exchange Registry. Studies held in centres across the US and Australia had similar findings and recommendations.[7,8,9]

Numerous public health problems have been raised by a Canadian study of transplant tourists.[10] There have been cases of patients presenting with multiple drug-resistant *Escherichia coli*, active tuberculosis, as well as other viruses and fungal infections not typically seen in Canada. The presence of multiple drug resistant bacteria certainly poses a domestic public health concern.

LEGALLY & SOME DEFINITIONS:

Under Section 279.04 of the Criminal Code of Canada, it is a criminal

offence to exploit another person and by the use of force, deception, or coercion remove their organs or tissues – be it domestically or internationally.[11,12] There is however currently no overarching federal law prohibiting Canadians from obtaining commercial organ transplants overseas, which were sold by a consensual donor.[13,14] In 2009, the House of Commons nearly passed Bill C-381 into law.[15] It sought to explicitly prohibit Canadians from going abroad to purchase an organ and would have criminalized any sort of participation, even indirect, in organ trafficking or transplant commercialism.

Bill C-381 would have also required health care professionals to report any patients of theirs who had undergone transplant tourism, much akin to mandatory reporting mechanisms already in place.[16] Some academics argue that simply banning this practice will not work.[4] To control an industry that has been roughly estimated to generate $600 million to $1.2 billion a year[3] in profits will be difficult, especially when a market of desperately ill and desperately poor people continues to exist. They contend that organ scarcity, which drives demand, needs to be dealt with by increasing organ donation via policies such as offering incentives for donation. However, it is hard to extrapolate these academics' arguments further, as it would otherwise lead to the unjustifiable position of allowing transplant tourism in some shape or form.

CONCLUSION:

Fundamentally, the issue of organ transplantation and commercialism is one of desperation-driven demand. Physicians should ensure that their patients understand the severe and frequent side effects of transplant tourism. They should explain the heinous facts – the various criminal organizations that the transplant trade funds, and the incredibly unethical nature of the trade, which is nothing short of the exploitation of the poor. These perils must be communicated early, before organ failure, so that patients do not act out of desperation. And if a patient with a commercial transplant comes into their care, they must simply remember their duty to minimize the patient's suffering and provide the best possible care for them.

The stakes are nothing more than the lives of the most vulnerable and distressed individuals in our communities and around the world.

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Matching theory: kidney allocation

Kyle Luong (Meds 2016)

Faculty Reviewer: Dr. Gregory Pavlov, PhD (Department of Economics)

ABSTRACT

Lloyd Shapley and Alvin E. Roth have recently been awarded the Nobel Prize in Economics for their work in matching theory. Although branching from the field of economics, matching theory has had many implications in the world of medicine. For example, the National Residency Matching Program in the United States is an application of matching theory. The focus of this article is the application of matching theory to kidney transplant allocation. Kidney transplantation is the best treatment for end stage renal failure. Unfortunately, the demand for kidneys exceeds supply. Kidney paired exchange programs, which have begun to garner great success in increasing the number of kidney transplants worldwide, base their foundations on matching theory. Overviewed in this paper will be how these programs were created and work, their successes, and some of the unique challenges and logistical obstacles they face.

INTRODUCTION

Traditionally, markets function with monetary exchange facilitating the movement of goods to buyers from sellers. However in some instances monetary exchange is unfeasible due to the nature of the market and as a result, prototypical market structure is inapplicable. Matching theory is a branch of game theory that deals with this non-price allocation. Pioneered by Lloyd Shapley in the 1950s and 1960s, it has been applied to real markets with great success. Two medical markets where matching theory has garnered this success are residency matching and kidney transplant allocation whose designs owe greatly to Alvin E. Roth, an American economist who made great forays into the application of Shapley's theories and their further development. Recently, both men were awarded the Nobel Prize in Economics for their work. In light of its contemporary step back into the public eye, this article will briefly outline matching theory with some examples from real markets. Finally, the application of matching theory to kidney transplant allocation will be explored, with a discussion of its success and future directions.

MATCHING THEORY: BASICS

Shapley's theory is based on stable matching. In their 1962 paper, Gale and Shapley demonstrated this idea with the stable marriage problem. [1] The stable marriage problem asked how a number of women could be matched to a number of men, considering their respective preferences for each member of the opposite sex. They showed that no matter the preferences, there would always exist a stable allocation. A stable allocation is one whereby no parties can be better off by further exchange. Stability is desirable in this example and its real world extrapolations as stability is seen as an indication of efficiency because further improvement of happiness from exchange is impossible. Additionally, stability imparts robustness to allocation systems since it eliminates incentives for parties to disobey or manipulate the rules of the system. In the stable marriage problem, the solution was the Gale-Shapley "deferred acceptance" algorithm. Suppose the men are allowed to propose to the women. Each man would propose to his favourite woman. A woman with more than one proposal would keep her favourite proposal 'on hold' without accepting, and rejecting all others. (Women with only one proposal would keep that proposal on hold as well.) With the second round of proposals, men who were rejected in the preceding round would propose to their second ranked woman. The women behave similarly as before, keeping their best proposal on hold and rejecting the rest, including any proposals from previous rounds. Eventually, all women will have been proposed to at which point they are all required to accept their on hold proposals. It was shown that all matches made in this manner were stable. An implication of the Gale-Shapley algorithm was that the proposing party would secure more favourable matches.

MATCHING THEORY: APPLICATION

At the crux of this deferred acceptance algorithm is free trading. In the stable marriage problem, the women were able to trade tentative proposals for anything better that came along. Although the marriage problem may seem contrived, it indeed has real world counterparts. One such market is residency matching in the US. Roth demonstrated that the matching algorithm used by the National Resident Matching Program (NRMP) was able to make stable matches because it was essentially an adaptation of the Gale-Shapley algorithm. [2] The allocation of residency positions was another stable marriage problem, with the hospitals proposing to the applicants. Harkening back to the stable marriage problem, Roth noted that the algorithm produced outcomes favouring hospitals. Moreover, with more physician couples wishing to match to the same areas, the algorithm was proving insufficient in meeting these new needs. In 1995, Roth and Elliot Peranson were enlisted to redesign the NRMP to accommodate couple matching. Their algorithm was adopted in 1997 and used ever since. [3]

KIDNEY TRANSPLANT

The best treatment for end stage renal failure is kidney transplant. Patients receiving transplants live 10 years longer than those on dialysis. [4] Unfortunately, the demand for kidneys outpaces the supply of deceased donors with over 70% of Canadians who are on organ waiting lists, needing a kidney. [5] Living donors are another resource, providing >16 years of dialysis-free survival compared to the 8.6 years from a deceased donor. [6] Unfortunately, the challenge with utilizing this pool of living donors was that many pairs of willing donors and recipients were deemed incompatible after screening. Information from these donors was usually not recorded for follow up and the pair would be sent home. [7] With such congestion on the deceased donor waiting list, there was an urgent need to better utilize living donors.

A solution to the problem would be another application of Gale

and Shapley's matching theory. Whereas the marriage problem and the NRMP represented a two-sided market (two parties matching with one another), the kidney exchange problem is one-sided as every individual and their initial donor candidate is regarded as a single item. Gale's top-trading cycle algorithm, which also produces stable matches, was the answer to this modified allocation problem. Objects are initially distributed to each entity and like the deferred acceptance algorithm, subsequent trading occurs. [8] In kidney transplantation, the initial allocation of objects is analogous to the pairs of incompatible donors and their intended recipients. Now, imagine two incompatible pairs of a donor and recipient. If each donor happened to be a match for the recipient in the other pair, a mutually beneficial exchange would be possible whereby both patients receive a compatible donor. This system of exchanges has been dubbed Kidney Paired Exchange (KPE). Exchanges could and have become more complicated, with further pairs participating in a daisy chain of trades. KPE has also been adapted to make use of the growing number of altruistic or non-directed donors. [9] In domino-paired donation, the altruistic donor donates the kidney to a recipient of an incompatible pair. The donor of said pair would then donate their kidney to a compatible recipient on the waitlist. Longer domino chains have been accomplished, with the longest to date spanning 30 kidneys and 60 individuals. [10]

SUCCESS

Since it was first suggested by Rapaport in 1986, [11] several informal exchanges have been reported. [12] Not until 2005 was the first national KPE program established in the Netherlands. [13] In the US, Roth helped design the New England Program for Kidney Exchange, [14] and along with the Ohio program was one of the early preludes to the national program proposed by UNOS in 2010. In Canada, a three province pilot program initiated in 2009 and has become nationwide as of October 2010. [15] The American programs have seen increased numbers of kidney exchanges in each subsequent year with >1000 cumulative transplants since 1998. [12] Researchers suggest that optimal utilization of the program could see as many as 1000-2000 additional transplants per year in the US; [16] saving the country $750 million USD in dialysis costs annually. [17] With the Canadian program still in its infancy, there is insufficient data to evaluate its success. To date, the Canadian Living Paired Donor Exchange Registry has facilitated 144 transplants with 14 more scheduled before the end of the year. Increased transplants mean more patients are experiencing a lessened burden of dialysis, better mortality, and a higher quality of life. [18]

CHALLENGES AND FUTURE DIRECTIONS

KPE program implementation elicits various challenges. One implication that arose was that all transplants would have to be done simultaneously to prevent donor reneging. Only recently have non-simultaneous donations been performed with altruistic donors being incorporated into non-simultaneous extended altruistic donor (NEAD) chains. NEAD resembles domino-paired exchange except the last donor in the chain does not donate to a waiting list recipient, but rather becomes a bridge donor, awaiting more pairs. Optimistically, the potential for extending the wave of exchanges outweighs the risk of donor reneging. Some argue however, to not be overconfident because of the honeymoon phase where a single donor is able to initiate a large chain of donations. Many chains will not propagate indefinitely and bridge donors accumulate as matches become rarer. Many drop out after some period of time. [19] A national KPE exchange also presents the need for co-ordination between the various transplant centers and a centralized registry. It is no surprise that additional viable exchanges are easier to find with a larger pool of pairs. However, there needs to be incentives for hospitals to enroll donor-recipient pairs instead of performing short chain exchanges internally. As well, the transport of donors across the country presents another challenge both logistically and financially. These are all issues that need to be addressed if KPE is to be used to its full potential.

CONCLUSION

This article has provided an introduction to matching theory and the ways it has been applied in real markets, with special regard to kidney transplant allocation. The discussion of KPE's permutations, successes and shortcomings here are definitely not exhaustive. For instance, the ethical issues associated with KPE have not been addressed here. Further reading is encouraged for those interested. Ultimately, matching theory proves to be applicable in many contexts, and has especially found some utility in the field of kidney transplantation.

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The role of prostate-specific antigen (PSA) testing in screening for prostate cancer

Charlotte Hunter (Meds 2015) and Paul Zamiara (Meds 2016)

Faculty Reviewer: Dr. D. Scott Ernst, MD, FRCPC (Department of Oncology, Division of Medical Oncology)

Prostate specific antigen (PSA) is a serine protease expressed mainly by the prostate gland and detectable in normal, benign hypertrophic, and neoplastic prostate tissue. While the majority of the PSA produced by the prostate gland is released into semen, a small amount (approximately one million-fold lower) normally leaks into the circulation and is detectable by immunoassay. In the hyper- and neoplastic prostate, though, its secretion into prostate ducts is lost and consequently more PSA is released into extracellular fluid and the circulation.[1] Serum PSA levels can therefore be used to track the growth or shrinkage of prostate tumors; indeed, the FDA approved its use to monitor cancer progression (i.e. tumor growth, response to treatment, recurrence) in already diagnosed men in 1986.[2]

PSA became the first biomarker (indicator of biological state) approved for screening asymptomatic men for cancer in 1994, when the FDA approved its use in conjunction with the digital rectal exam (DRE) to screen for prostate cancer. A PSA level of 4.0 µg/L was traditionally considered the upper limit of normal, and a prostate biopsy was recommended to patients exceeding this level. However, prostate cancer screening based on PSA level has limited specificity (33%, versus 86% sensitivity[3]), as inflammation (prostatitis) and benign growth (benign prostatic hyperplasia) of the prostate will also elevate PSA levels.[2]

Therefore, despite the PSA test's utility in monitoring tumor progression and response to treatment, its use as a screening test for prostate cancer in asymptomatic men remains controversial. Because of the considerable public health burden imposed by prostate cancer – it was the most diagnosed cancer in males in 2008 (about 899 000 cases and 258 000 deaths worldwide), with 72% of cases occurring in developed countries[4] – proper screening tools and guidelines are extremely important.

The Canadian Cancer Society has suggested that the benefits of having a PSA test for screening purposes include the peace of mind granted by a normal result; identification of those in need of further testing (if the result is higher than expected for the patient's age); and the ability to detect prostate cancer before it is symptomatic and/or before it has spread beyond the prostate.[5] However, they also point out the potential for harm associated with prostate cancer screening, such as the unnecessary anxiety caused by a false positive; the potential for a false negative and the propensity to then ignore worrisome symptoms that may emerge later; and the risks associated with treatment of slow growing prostate cancer that could have been left alone.

The current guidelines for prostate cancer screening in Ontario state that PSA testing should not be used as a population-wide screening tool for early detection of prostate cancer in asymptomatic men.[6] Instead, physicians should discuss the benefits and potential harms of testing with men who are between the ages of 50 and 75 and have a life expectancy of at least 10 years. This discussion should also include men over 40 with a first degree relative who has had prostate cancer, and men of African ancestry. With this information, men can then decide for themselves whether they would like to undergo testing. A PSA value >4.0 µg/L or an abnormal DRE warrants further investigation.

Dr. George Kim (personal communication, December 4, 2012), a family physician working in Southwestern Ontario, restricts his ordering of PSA tests to symptomatic men. In the event of a worrisome change in prostate-related symptoms (i.e. increased urinary urgency or frequency, or poor urinary stream with urinary tract infection unlikely, especially when the patient is of African descent or has a first degree relative diagnosed with prostate cancer prior to age 65), he prefers to send patients for prostate ultrasound and possible biopsy. However, Dr. Kim finds the PSA test to be a convenient test in the interim if the ultrasound cannot take place within 10 days. In terms of screening, Dr. Kim believes patients would like to undergo a simple test, like the PSA test, that could definitively detect cancer; because of this desire for certainty, patients may have unrealistic expectations regarding the validity of test results. He therefore recommends discussing with patients the advantages and limitations of PSA testing (including its low specificity), and explaining why it cannot replace other surveillance methods (i.e. the DRE).

Taking a more extreme stance than the Ontario guidelines, the U.S. Preventive Services Task Force recently recommended against any PSA-based screening for prostate cancer, regardless of age, based on their conclusion that many men are harmed by this screening test and few benefit from it.[7] The Task Force's conclusions were largely based upon two ongoing studies: the U.S. Prostate, Lung, Colorectal & Ovarian Cancer (PLCO) Screening Trial and the European Randomized Study of Screening for Prostate Cancer (ERSPC).

The PLCO trial involved 76 693 men between the ages of 55 and 74 who were randomized to annual PSA screening for 6 years, combined with a DRE for 4 years, or care as usual.[8] A PSA value >4.0 µg/L was used as the cutoff for a positive screen result. The incidence of prostate cancer was significantly higher in the screening group after 7 years of follow-up (RR, 1.22 [95% CI, 1.16-1.29]), but there was no significant difference in prostate cancer mortality (RR, 1.13 [95% CI, 0.75-1.70]). The 10 year follow-up data, while only 67% complete, was also consistent with these findings.

The ERSPC trial randomized 182,000 men between the ages of 50 and 74 to either the screening group, which received a PSA test every 2-7 years (depending on the centre), or the control group, which received care as usual.[9] Most centres in the trial used a PSA cutoff value of 3 µg/L, with a positive screen result warranting a biopsy. After a median follow-up of 9 years, there was no statistically significant difference in prostate cancer mortality between the men assigned to the screening group and the controls (RR, 0.85 [95% CI, 0.73-1.00]). However, in a

prespecified subgroup of 162 243 men aged 55 to 69 there was a significant absolute risk reduction in prostate cancer mortality for the men assigned to screening (RR, 0.80 [95% CI, 0.65-0.98]).

Beyond the fact that the results of these two trials do not provide us with a consistent answer to the question of whether PSA-based screening reduces prostate cancer mortality, the U.S. Preventive Services Task Force was somewhat critical of the methods used in these trials. Both trials failed to exclude men who had had previous PSA testing, the PLCO trial had substantial contamination of the control group (up to 52% of controls received a PSA test during the trial), and the ERSPC trial used a range of PSA cut-off points (>2.5 to 4 μg/L) and screening intervals depending on the centre.[10]

The Task Force's decision-making was also influenced by harms associated with PSA-based screening. For example, 75.9% of men who underwent a biopsy because of an elevated PSA value in the ERPSC trial had received false-positive results.[9] Complications of diagnostic evaluations occurred in 68 of 10 000 procedures in the PLCO trial, and included bleeding, infections, and urinary difficulty.[8]

Given the uncertainty surrounding the interim results of these two major trials, it will be important to see whether longer-term follow-up of the study participants conveys a clearer message about whether PSA-based screening reduces mortality. Even with the current evidence, the Task Force's strict recommendation against any PSA testing for screening purposes has been criticized for preventing patients from being involved in decision-making.[11] In a New England Journal of Medicine commentary written in response to the Task Force's report, Drs. McNaughton-Collins and Barry (two prostate cancer specialists affiliated with Harvard Medical School and Massachusetts General Hospital) argued for a strategy similar to Ontario's guidelines in which patients are made aware of the benefits and harms associated with PSA-based screening and are able to decide for themselves whether the potentially small benefit is worth it to them.[11] However, they also suggested that if physicians continue to order PSA tests for screening purposes they must do a better job of emphasizing the potential harms associated with PSA testing, rather than touting only the benefits of screening. Physicians must also make sure that they are not overtreating patients who might benefit more from a "watchful waiting" approach.

Thus far, measurement of absolute PSA level for the purposes of prostate cancer monitoring and screening have been discussed. There are other measurements to increase screening specificity that are currently being explored. A recent retrospective cohort study evaluated the utility of a measure called the PSA velocity (PSAV) risk count in 18 214 men enrolled in a prostate cancer screening study.[12] PSAV refers to the yearly change in PSA units, and the risk count is a measure of the number of times PSAV exceeds 0.4 μg/L. A PSAV risk count ≥ 2 (i.e. two consecutive yearly increases in PSA levels exceeding 0.4 μg/L) showed 96% specificity (compared to the reported 33% specificity for the absolute PSA level[3]) and was associated with a significantly increased risk of prostate cancer (OR 8.2 [95% CI, 7.0-9.6]). In this study, the odds ratio for prostate cancer determined by PSA level, in contrast, was only 1.25 (95% CI, 1.22-1.28). These results suggest that further investigation of PSAV utility in prostate cancer screening is warranted.[12] The US National Cancer Institute also lists PSA density of the transition zone (PSA level divided by the volume of the prostate's transition zone) and age-specific PSA reference ranges as parameters under investigation for improvement of PSA screening specificity.[2] While these alternative screening options are being investigated, Ontario's recommendation that patients should be properly informed about PSA testing and encouraged to participate in decision-making seems appropriate.

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The living kidney donation process: role of the interdisciplinary team

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INTRODUCTION

End stage renal disease (ESRD) is becoming an increasingly prevalent illness in Canada.[1] The Canadian Organ Replacement Register Annual Report released by the Canadian Institute for Health Information (CIHI) stated that the number of Canadians living with ESRD has tripled from 1990 to 2009.[1] Unfortunately, the number of kidneys donated has not kept pace with this increase in demand. In 2009, approximately 38,000 Canadians are living with ESRD, with 59% on dialysis, and 3,000 patients on the transplant wait list.[1] The increase in dialysis treatment also comes with a substantial cost to the health care system – the estimated cost for hemodialysis is $60,000 per patient, per year.[1] The CIHI estimates that a renal transplant saves the health care system $250,000 per patient over a five-year period.[1]

Due to the shortage of cadaveric kidneys, there has been an increase in using donations from living donors, often from an offspring, parent, or other genetically related family members. Donations from unrelated donors also make up 30% of the donation pool, with a portion being strangers to the recipient. Several studies have shown that patients receiving living kidney donations from either genetically related and unrelated donors achieve better outcomes than patients receiving a kidney transplant from cadaveric donors.[3,4,5] Living-donor transplantations have been shown to be associated with a shorter time to transplantation, and results in a better long-term graft and patient survival.[6] As a result of the increasing importance of living donation, protocols have been developed to accommodate living donations: Live-Donor Paired Exchange, Live-Donor/Deceased-Donor Exchange, and Altruistic Living Nondirected Exchange.[2] In the Live-Donor Paired Exchange, a donor-recipient pair (the patient requiring a transplant, and a willing donor who cannot provide a matching kidney) is matched with another donor-recipient pair such that a compatible donor-recipient exchange is made. This matching process, or chain, is continued until all recipients receive a kidney. In the Live-donor/Deceased-donor exchange, a donor-recipient pair is reassigned such that the live-donor is matched with a recipient already waiting on the deceased donor list. In exchange, the first recipient is moved nearer to the top of the cadaver list. Finally, the Altruistic Living Nondirected Exchange is true to its name—the kidney donation comes from a generous person who is a stranger to the recipient.

To provide sufficient care for both the donor and recipient, a large multidisciplinary team is required to address different facets of care, including processes of donation, matching, and maintenance of care. This article will discuss the living kidney donation process, as well as the role and importance of the multidisciplinary team.

THE MATCHING PROCESS

The Living Donor Paired Exchange is a program run through the Canadian Blood Services that identifies matches between potential living kidney donors and transplant recipients in Canada.[7] Matching refers to the tests carried out by clinical scientists prior to transplantation to minimize the risks of acute or delayed graft rejection. This involves ensuring the blood type of the donor and recipient are compatible, testing the histocompatibility of the donor kidney, and screening the plasma of the recipient for antibodies against donor kidney cells.[8] To test for histocompatibility the surface molecules present on the donor and recipient cells, specifically human leukocyte antigen (HLA) complexes, are compared and assessed for similarity.[9] Higher similarity between donor and recipient HLA complexes are associated with increased long term survival rates, and a decreased chance that the immune system of the recipient will identify the donor cells as foreign.[9] Individuals may have antibodies against HLA complexes circulating in their blood due to past transplants, pregnancies, or blood transfusions where their immune system was exposed to foreign human cells.[10] This is why the plasma of recipients must be screened for antibodies targeting donor cells prior to transplantation in a process known as cross matching.[10]

THE LIVING KIDNEY DONATION PROCESS

In this section we will focus on several components of the organ donation process including assessment of the living donor, informed consent, and follow-up. These steps typically involve the presence of a transplant coordinator, physician, social worker, psychologist or psychiatrist, and surgeon. Furthermore, throughout the entire process there is usually a designated living-donor advocate who is experienced in the field of transplantation. The advocate can be a social worker, coordinator, psychologist, psychiatrist, or physician. This advocate should advise the donor independent from recipient interests.[2]

Assessment of the living donor

The process for determining donor acceptability may vary between transplant programs. According to guidelines outlined by the Multi-Organ Transplant Program of the University Health Network (UHN) in Toronto, separate health care teams assess potential living donors and recipients. Ideally, this would include each donor and recipient with his/her own physician, coordinator, social workers, and psychiatry staff. This is done to avoid potential conflict of interests. The criteria for assessment include low medical/surgical risk, ability to give informed consent, realistic expectations of donation, voluntary motivation, and sufficiency of economic, practical, and emotional resources to cope with the donation process.[17] The assessment process includes a full physical evaluation to ensure that the donor is healthy and that there are no major risk factors that would lead to renal disease in the future. The donor is also evaluated for psychological and social barriers to donation.[2] This process requires involvement from all members of the multidisciplinary team. Similar processes exist across Canada within other multi-organ transplant centres.

In the case of a dispute within the transplantation team about the suitability of a potential donor, the team may review the criteria used to measure suitability. Additional sources of input may include advice from other professional members of the staff, hospital ethics services, legal counsel, hospital administrative resources, or outside hospital consultation.[17]

Informed consent

Informed consent involves confirming the patient's capacity to understand and consent, disclosing information about the proposed procedure, and ensuring voluntariness. In the context of organ donation this involves a detailed discussion of the risks and benefits to the living donor and recipient. The potential donor should be informed about alternative treatment options for the recipient as well as the possible impact of donation on the donor's lifestyle, family relationships, finances, future employment, and ability to receive life insurance. Donor and recipient are typically provided with general information and details on program-specific outcomes.[17]

When a donor appears undecided, counselling can be offered by a social worker or psychiatrist to assist the potential donor to solve problems and address psychosocial aspects of this decision such as emotional issues and how to inform others. Potential donors should be informed that they can withdraw from the process of donation at any time with the full support of the transplantation team. A crucial part of the assessment process is to ensure that the donor is making his or her decision free from coercive or manipulative influences.[17]

Follow-up

It is important to evaluate donor and recipient experiences including medical, psychosocial and economic outcomes. According to UHN guidelines, early and late morbidity, graft function, mortality rates and measures of recipient and donor satisfaction are documented in an annual review. In the event that a donor requires further care, appropriate care is arranged.[17]

THE IMPORTANCE OF THE INTERDISCIPLINARY TEAM

As outlined by the previous section, the interdisciplinary team plays a crucial role in every step of the donation process. In addition, there has been a growing body of evidence showing the benefit of interdisciplinary involvement on quality of patient care (both donor and recipient), patient satisfaction and survival. In particular, a paper by Winsett and Hathaway identified three areas of intervention that will increase the patient's quality of life post-transplant: post-transplant adverse events, employment, and social support.[11] Literature has shown interdisciplinary teams have been beneficial for providing support for the patient and their family pre- and post-transplant. At the Queen Elizabeth II Health Sciences Centre in Halifax, it was shown that a multidisciplinary kidney disease clinic consisting of nephrologists, nurse educators and dietitians was able to improve metabolic and blood pressure control, and facilitate the use of peritoneal dialysis in late referrals for patients with chronic kidney disease.[12] In a study by Fonouni, Golriz, Mehrabi, et al., an interdisciplinary team consisting of a transplant surgeon, a nephrologist, a pediatrician, a radiologist, a psychologist, a transplant coordinator, and a transplant nurse was shown to have improved staff communication, patient outcomes and satisfaction with the hospital stay.[13] Several studies also showed an increase in favourable mental and physical outcomes post-transplant with the involvement of an interdisciplinary team.[14,15,16]

CONCLUSION

The increasing prevalence of end stage renal disease and the shortage of cadaveric kidneys underline the growing importance of living kidney donation. However, living kidney donation is a complex process that merits careful ethical consideration. This process involves collaboration between multiple health care professions on the side of the donor and the recipient. Health care workers should have an understanding of different aspects of support that are involved in kidney donation in order to inform others and alleviate anxiety surrounding kidney donation. Several studies have already demonstrated that the current shift towards a more integrated and multidisciplinary approach in kidney transplantation improves patient care, satisfaction, and survival. Therefore it should be made clear that the preparation and ultimate outcome of kidney transplantation does not depend solely on the efforts of a nephrologist or transplant surgeon, but rather a team effort.

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The future of surgical robotics

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Robotic surgery is a growing technology with the potential to revolutionize surgical procedures, especially in the field of urology. Urology is at the forefront of advances in this field, and has integrated robotics into many procedures including radical cystectomies, surgical nerve grafting and pyeloplasty.[1] Robotic surgery has almost entirely taken over radical prostatectomy and the role of robotics is continuously expanding. Robotic surgery helps improve patient outcome by minimizing the surgeon's movement tremors, increasing range of motion, decreasing blood loss, decreasing length of hospital stay, and decreasing post-operative pain.[2,3] Since the field of Urology deals with very difficult and delicate procedures, robotics offers an advantage by allowing for greater accuracy, flexibility, smoother actions, and greater range of motion.

An important area of advancement for surgical robotics is in the field of imaging and visual feedback. Robotic surgery can be performed either with a surgeon controlling the robot such as is done with the da Vinci system to perform robotic-assisted radical prostatectomies (RARPs), or autonomously based on a predetermined algorithm such as in the case of radiosurgery for pituitary adenomas.[4] While autonomous robotic systems offer higher precision, and tissue-damage avoidance, surgeon-controlled systems are much better at decision making in unstructured or chaotic situations. For the surgeon controlling the robot, visual feedback can be attained using endoscopic cameras; however, for autonomous procedures, the control program requires much more detail about the patient's anatomy.

Generally speaking, there are two types of imaging performed for robotic surgeries: pre-operative and intra-operative. Pre-operative imaging is acquired before a procedure and used for surgical planning to locate pathologies, a feed-forward system. In computer-guided systems this can be problematic since the images which are used for instrument navigation are based on tissue location at the time of imaging. However, instrument deflection caused by instrument-tissue interaction as well as tissue movement can mean that the instrument position is not as precise as is desirable. This is especially problematic when dealing with smaller anatomical targets, such as vascular surgery and in paediatrics.[5] Intra-operative imaging is used to provide close to real-time feedback, thereby closing the feedback loop and allowing for adjustments throughout the procedure. While for surgeon controlled robotics, surgeons have the flexibility of compensating via visual feed-back, for autonomous computer-controlled systems this cannot be as easily implemented due to the need for code to interpret the visual feedback into a control for the robot.

Research into methods of providing a closed-loop feedback system which takes into account instrument deflection and tissue movement has been carried out using various approaches. Methods of measuring instrument position include computer vision techniques,[6] and electromagnetic sensor systems.[7] This information then needs to be integrated into the computer control system to allow for changes in position as the surgery progresses. This has been achieved using Direct Image Guided Intervention (DIGI) robots. These robots use pre-operative images to locate targets and create an initial navigation protocol. They are also connected to an imaging modality which allows for real-time adjustments to this protocol, providing greater accuracy and precision than a feed-forward system. Some challenges to DIGI include compatibility between robot and imaging modality such as MRI which has a dense magnetic field, and most components of the robotic system cannot be safely used in proximity to the magnet. Other problems include spatial resolution, and exposure to radiation if fluoroscopy or CT is used.[8] The Robarts Research Institute at Western University is investigating the use of two-dimensional transrectal ultrasound (TRUS) to create three-dimensional real-time images by sweeping the probe about its axis. This technology has been combined with surgeon operated robotic surgery for urologic procedures such as prostate brachytherapy or biopsy.[9]

Another area of research with the potential to improve computer assisted surgery is haptics. Haptics is the general term used for touch feedback. This includes both tactile feedback (i.e. temperature, vibration, texture, etc) and kinaesthetic feedback (i.e. force and position). The majority of the work done regarding haptics in surgical robotics is surrounding kinaesthetic feedback, rather than tactile feedback.[10] A known drawback of robot assisted minimally invasive surgery using such surgical robots is the lack of haptic feedback.[11-13] This drawback has been found to be most limiting during complex tasks and can lead to difficulty identifying tissue based on consistency (i.e. between normal and tumour tissue) and suture breakage during knot tying.[14-18]

The reason for the lack of haptic feedback in such systems is simple: the technology required is incredibly complex. The problem of providing haptic feedback can be broken down into two distinct tasks: measuring the interaction forces and displaying these forces to the surgeon. Measuring of interaction forces during robotic surgery has been attempted in a few different manners. Retrofitting existing surgical manipulators with commercially available force sensors has been attempted;[19] however, constraints regarding size, geometry, biocompatibility, sterilizability and cost have limited this approach.[10] Another method is to use the distance between desired position and actual position of the manipulator to determine force interactions between the manipulator and the environment. This method has been implemented with some success; however, it is limited by the non-ideal nature of the robots and the environment, meaning that friction and other dynamic forces are difficult to account for and can be large in comparison to the interaction forces between the manipulator and the patient.[10,20]

Methods of providing feedback to the surgeon include direct force feedback where motors in the robot controls are programmed to recreate the forces sensed by the manipulator, and the use of other sensory

feedback such as audio or visual feedback to represent the forces experienced by the surgical instrument. The first method is the most commonly implemented method;[10] however, enabling a system to provide force feedback in all directions actuated by the system (i.e. six degrees of freedom plus gripping) is not possible without implementing a second feedback system.[22] Use of motors to provide feedback also introduces the possibility of feedback instability which can lead to uncontrolled oscillations, an obviously undesirable event during surgery.[10] To get around these problems, various groups have attempted to implement feedback systems using visual or audio displays of force.[14,23-25] These systems have experienced some success and have potential for further implementation as long as they do not interfere with the surgeon's view of the tissue through the video display of the endoscopic camera.[10]

Robotic surgery allows precise and repeated motions with decreased fatigue, smoother actions and increased accuracy, flexibility, and range of motion, especially in small confined anatomical locations such as the male pelvis during prostate surgery. However, there are still limitations in visual and haptic feedback. These limitations, as well as training of surgeons, have stunted the growth of this field in some ways; however, as described, intensive research is underway. It is clear that in certain situations, it is best to rely on image guidance, allowing the surgeon to be guided by more than what is visible through the visual field. For this to happen, imaging modalities which allow for greater compatibility with the surgical robot while maintaining as low radiation dose to the patient and surgeon as possible will need to be developed beyond the current technology. Similarly, to better enable this physician to identify specific tissues, haptic technology and its implementation into surgery will also need to be furthered. As these technologies become increasingly incorporated in the field of surgical robotics, we can expect rapid growth in the number of surgeries to make the transition from traditional to robotically-assisted or even fully automated.

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Interview with Dr. Faisal Rehman

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Faculty Reviewer: Dr. Faisal Rehman MD, FRCPC, M.Ed (Department of Medicine, Division of Nephrology)

Stepping into Dr. Faisal Rehman's office, we could not help but notice the countless degrees, teaching awards, photographs and thank-you notes that decorated his walls. On a Friday afternoon, we were lucky to sit down and speak with the distinguished clinician, teacher and boxer at the Schulich School of Medicine & Dentistry.

As the Nephrology Site Chief and the Director of Internal Medicine clerkship program at University Hospital and chair of the genitourinary block in the first-year curriculum, Dr. Rehman has a longstanding history with Western University. After completing a Bachelors degree in pharmacology at the University of Alberta and a Medical degree at Queen's University, Dr. Rehman began his training in internal medicine at Schulich. He completed his nephrology fellowship in 2001 and went on to pursue a Masters of medical education at the University of Toronto. Dr. Rehman returned to Western University where he has since established a rewarding and successful academic medical career.

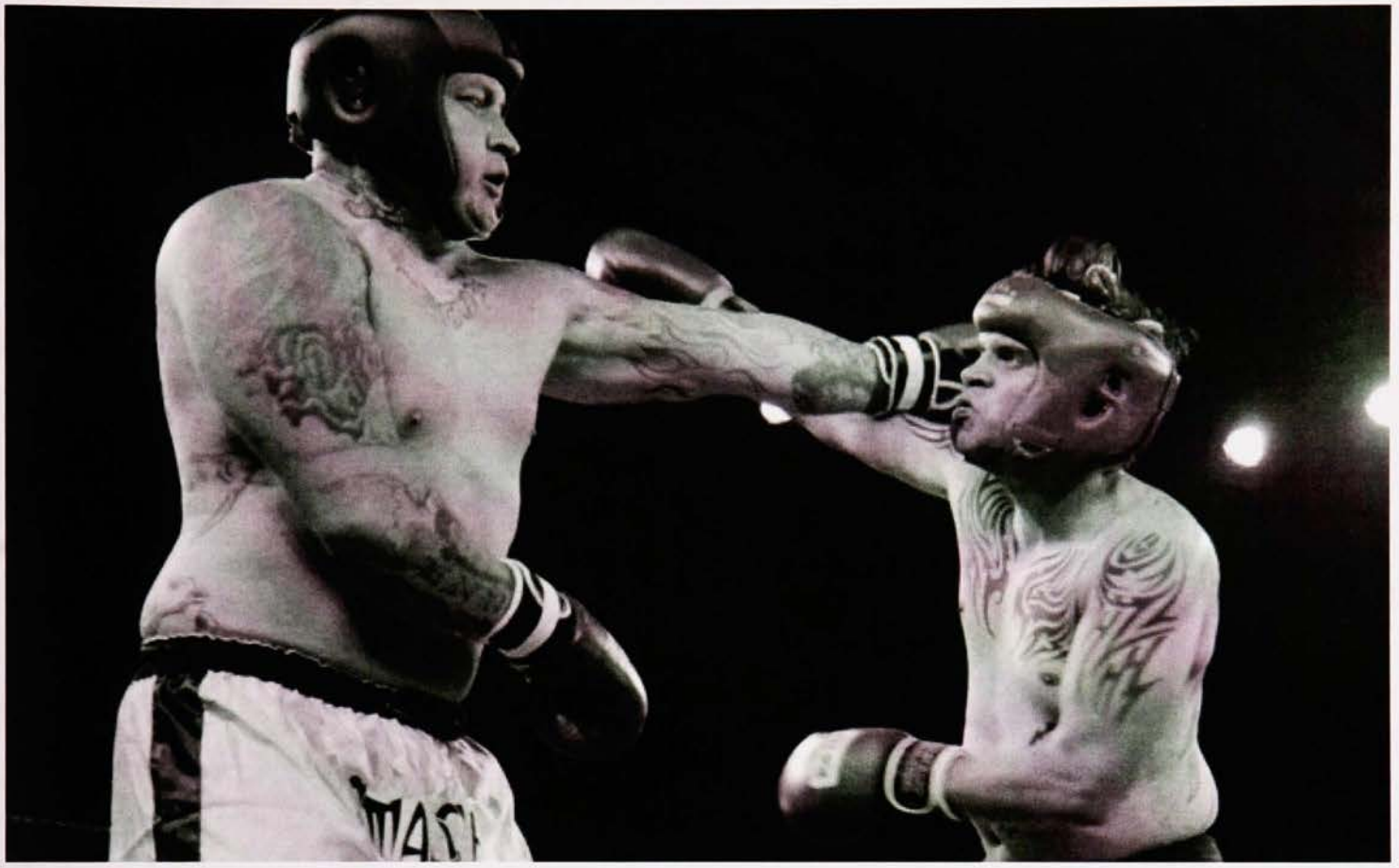
Dr. Rehman developed a fascination with medicine at a young age under the influence of family and friends in the profession. He set his mind on internal medicine after exploring clinical observerships but admitted that choosing a specialty was a more difficult challenge than being accepted to medical school. Dr. Rehman recognized near graduation that intellectually stimulation through problem solving was what he enjoyed most in medicine, leading him to choose a residency in internal medicine. Internal medicine's range combined with Dr. Rehman's interest in longitudinal care ultimately drew him to the field of nephrology. He loves nephrology, he tells us, because it involves complicated physiology, offers diversity – from transplants to glomerular nephritis to diabetes – and allows him to help patients in various stages life: from disease in the outpatient clinic to dialysis, to transplant, to transplant failure and return to dialysis.

When asked about the future direction of research in his field, Dr. Rehman says he sees portable artificial kidneys helping restore independence and improve quality of life for the chronic hemodialysis patients he works closely with. He is hopeful new kidney technology could be translated into clinical practice since dialysis is an inconvenience and unpleasant experience for patients. In addition, Dr. Rehman believes that the delivery of care needs to be altered to accommodate the increasing prevalence of chronic kidney disease. "Unless we can have novel inventions like the artificial kidney, I see our dialysis population exploding. I see our CKD (chronic kidney disease) clinics being overwhelmed. Unfortunately disease prevention has not gotten a lot of hype."

As for what he enjoys most about his career, Dr. Rehman's response was strongly echoed by the awards on his walls: "I love to teach," he says, and especially being around students to teach them in the early stages of their careers. In addition to traditional teaching in the classroom, he has served as honorary president of the Hippocratic student council and other class councils. Even his research interests complement medical education. The projects he has overseen have included artificial kidney modeling, training renal fellows and developing nephrology-related research filters. In his words, "the best reward is to see a student mature and develop to the point they know more than you. And I've seen that in my students who are now consultants who have really excelled in research or medical education. It makes you proud that you have contributed to that person developing."

We could not leave Dr. Rehman's office without satisfying our curiosity about his charity boxing career that lent him the name King Faisal. Outside of medicine, the physician indulges in boxing, which he enjoyed watching as a child and training in as a youth. When the department needed to raise money for kidney research 5 years ago, Dr. Rehman volunteered to raise money for the Kidney Clinical Research Unit, thinking at the time, "If I'm going to do this, I will do my kind of event." With the help of a friend who was an international boxing champion, the first Knock Out Kidney Disease annual gala was put together in a little over a year in 2008. Not only did Dr. Rehman mastermind the organization of the event, he also trained to fight in the ring in order to raise more money. His initiative and training paid off in a huge way: the event has raised over $600 000 over the past 4 years for the Kidney Clinical Research Unit and the Mathew Mailing Centre for Transitional Transplant Studies at University Hospital.

Dr. Rehman also shared with us one of his most memorable patients, which was an incredible case of human resilience. This patient was Ms. AL, a single mother of five young children, who suffered from systemic lupus erythematous (SLE) and presented with severe skin rash, hematouria, and proteinuria. Even though her kidney disease of membranous lupus nephritis was initially managed accordingly with immunosuppressants, she started to develop severe hemoptysis secondary to lupus vasculitis of the lungs. She experienced further worsening of kidney function (acute kidney injury) and required multiple transfusions of 20 to 30 units of blood. Any further management of immunosuppression and plasmophoresis just seemed to make matters worse. She had a prolonged hospital stay of 2 months, developed myocarditis and lost a significant amount of weight that severely limited her mobility. But just when the story could not get any worse, the patient suddenly got better. She started to recover after Dr. Rehman stopped one of her immunosuppressive medications. Now, she leads an active and full life, does charity work for a lupus society and is healthy enough to travel all over the world. Dr. Rehman can only speculate that perhaps the powerful immunosuppression meant to control her lupus had essentially functionally ablated her bone marrow as a side effect. It was a memorable case for him because she had been so close to death but then spontaneously got better with no more signs of lupus. He says, "this case helped to reinforce that I need to constantly re-evaluate what I'm doing, and to not stick to a recipe. It



made me realize that medicine is an art for some patients."

For any medical students considering the field of internal medicine and perhaps nephrology, Dr. Rehman has some words of wisdom to offer. "In my opinion nephrologists are the classic internists. They have to know everything about the body," he says. A nephrologist is someone who enjoys complicated physiology and longitudinal care of patients. Nephrologists work in a unique field where patients can never be signed off. They may need to be followed from age 10 to 12 years old until death and everything in between: from dialysis, a transplant, back to dialysis, and through family catastrophe. Lastly, he tells us that, "the first few years of medical school are not conducive to learning about what you want to do when you grow up. What I found helpful is to really maximize the opportunity to do observerships to get a flavour of what's involved to make a better decision. Trying to narrow it down between surgery and medicine upfront may be helpful."

Although many clinicians lead rewarding academic medical careers, few can claim their students know them as King Faisal. Dr. Rehman exemplifies how extensive a physician's involvement in medicine can be. His involvement in patient care, medical education, student initiatives, research and fundraising all reflect his diverse passions and speak to his ability to maintain balance in his life and career. It is clear that Dr. Rehman loves what he does and his patients and students clearly appreciate all the time he gives.

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Fever with incontinence in the elderly: an approach for emergency medicine

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Faculty Reviewer: Dr. Derrick Pringle, MD, FRCPC (Division of Emergency Medicine)

A 72-year-old man develops a high fever and is taken to the ER by his concerned wife and daughter. During the intake interview, the wife reports that the man is experiencing worsening incontinence and occasionally complains of dysuria. Past medical records indicate that the man is already being treated and followed for hypertension and early Alzheimer's disease, but the wife notes that it has become increasingly difficult to manage her husband's confusion over the past week.

An emergency physician receives the above information from the triage nurse. The nurse adds that the man and his family have been waiting for two hours and all three appear quite distressed. How could such a situation be managed?

GERIATRICS AND DEMENTIA: CONSIDERATIONS FOR THE BEDSIDE

The age of a patient carries important implications for patient assessment and treatment. The physiology of a healthy, older adult adapts to functioning with tissues that have deteriorated with age, achieving a state of compromised balance termed homeostenosis.[1] Patients in this subpopulation thus have a reduced capacity to respond and adapt to the stresses brought on by acute illness and are more vulnerable to such insults.

This affects patient assessment, as it may be difficult to distinguish symptoms of underlying disease from those of acute illness. Determining the patient's medical history, current medication regime and social circumstances is also challenging in an emergency setting.[2] Prospective treatments are limited in that they must not exacerbate or interact with existing conditions and treatments. Polypharmacy, in particular, disproportionately affects the elderly and contributes to increased adverse drug events, physician visits, emergency admissions and hospitalisations.[3]

All the above can be further complicated by dementia in the patient. The patient's history may need to be obtained from family members or caregivers present in the ER or staff at a care facility, potentially leading to mistakes in interpreting symptom severity or missing incipient problems entirely. Furthermore, the patient may be unwilling or unable to participate in diagnostic or interventional measures that become indicated through the course of care.[4]

Pain management is especially difficult and no less important for patients with dementia. Though not ideal, primary care physicians must take care to detect surrogate markers of pain, such as confusion, gesturing or posturing, through the physical examination.[4]

Returning to the case, it is determined upon examination that the patient does not have the capacity to make his own medical decisions when he is unable to give his own name. Fortunately, his wife and daughter are attentive and meticulous principal caregivers. On request, they produce a list of medications the patient is taking currently (chlorthalidone and ramipril for hypertension, galantamine for dementia, cyclazine for nausea, loratadine for seasonal allergies) and confirm that this degree of confusion is highly atypical. Unexpected change in cognitive status is a hallmark of pain in dementia, so 1000 mg acetaminophen is ordered,[5] after establishing that the patient would have no known allergy or drug interactions. Vital signs are assessed and no abnormalities beyond high blood pressure (145/90) and high oral temperature (40.5 °C) are found.

SIGNS OF INFECTION IN THE ELDERLY

Fever as a sign of infection can operate quite differently in older adults. Ageing-mediated impairment of thermoregulation means that fever can fail to occur in up to half of elderly persons, despite the existence of life-threatening infection. Even normal body temperature can be lower than expected in the elderly and even lower in those with dementia, due to the same age-related changes.[6]

Given the above, the finding of fever in the patient is a definite cause for concern. An explanation for this sign is sought in the next prominent set of symptoms: worsening incontinence and dysuria.

URINARY INCONTINENCE: DIFFERENTIAL DIAGNOSIS

Age is the greatest determinant of urinary incontinence risk. Many factors that negatively affect normal micturition are more likely to occur with increasing age. With respect to transient incontinence, these include urinary tract infections (UTIs), genitourinary muscle pathology, acute illnesses that mandate immobilisation or catheterisation, fecal impaction, medications with autonomic effects or psychological expression of dependency or rebellion.[7]

Though females are much more likely to experience incontinence than males, several urological causes of incontinence are exclusive to males. For younger males, in particular, urethral and prostatic infection secondary to a sexually-transmitted disease is a frequent cause of incontinence.[8] In older men, incontinence is more often related to prostate disease. Prostate surgery is the most common cause of stress urinary incontinence in men and prostate hypertrophy may cause overflow incontinence by compressing the bladder.[9] More importantly, UTIs are much more common in older than younger men, with an incidence approaching that seen in women.[8]

In the emergency department, life-threatening causes such as cauda equina syndrome, spinal cord compression and paraspinal abscess must additionally be ruled out if suspected. A bacterial abscess could be consistent with typical infection-related observations, like fever, and can lead to both the other conditions by direct or vascular compression. An MRI is necessary for ruling out this possibility.[10] If additional lower body motor or sensory symptoms are present, it is important to more definitively determine whether the cauda equina or spinal cord is af-

fected.[11]

In the present case, the physical examination is continued with an awareness of possible urological disease. Palpation of the abdomen does not reveal a distended or swollen bladder, which would have suggested overflow incontinence.[7]

As fever, dysuria and incontinence together point convincingly toward a urologic problem, an abdominal CT scan is not indicated at this point. Instead, blood is drawn for routine chemistry. A urethral catheterisation is performed to obtain a sterile urine sample for urinalysis and urine culture. The patient is mildly uncooperative but accepting of oral medication, so oral sedatives are administered.[12] A bedside ultrasound bladder scan is ordered to rule out urinary retention and the need to leave the catheter *in situ*.[13]

An hour later, several reports are forwarded from the laboratory. Blood urea nitrogen (BUN) and creatinine are both normal, indicating good kidney function, especially for the patient's age.[14] The routine urinalysis report, on the other hand, shows bacteria and leukocytes in high numbers in the urine (bacteriuria and pyuria) and the nitrate test is positive. This and urine turbidity shift suspicion to urinary tract infection (UTI) as opposed to the more common urethritis.[8] Armed with all of the above, the doctor returns to the bedside.

URINARY TRACT INFECTIONS: DIAGNOSIS

In the elderly, investigation for UTIs needs to be justified by a high degree of suspicion because urinary incontinence and dysuria alone are very common and non-specific, as discussed. In fact, conditions like pollakiuria (frequent urination) and nocturia (night urination) are estimated to be present in over 50% of individuals over 60 years of age.[15] In this population, even individuals without infection often present with the classic triad of UTI diagnosis: frequency, urgency and dysuria.[16]

Diagnosis of UTI in an older adult, then, often depends on non-urological indications. These commonly include a general decrease in day-to-day function, loss of weight or appetite, decreased alertness or flank or abdominal tenderness. For patients with dementia, behavioural deterioration and confusion can be extremely important symptoms.[16]

For the current patient, fever, confusion, dysuria and incontinence create a strong suspicion of UTI, strengthened by the subsequent findings of bacteriuria and pyuria. Upon further questioning, the daughter additionally confirms that lately the patient's appetite has decreased noticeably.

URINARY TRACT INFECTIONS: MANAGEMENT IN THE ELDERLY

Diagnosis and treatment of UTIs in the emergency department frequently occurs without formal bacteria culturing.[17] Though it is possible for asymptomatic urologic bacteremia to resolve spontaneously in the elderly, serious complications like renal damage, pyelonephritis and sepsis may occur, so it is prudent to treat all UTIs in the elderly as complicated.[16, 17]

For most cases, a 10- or 14-day course of the broad-spectrum antibiotic levofloxacin is indicated. Particularly for elderly men, a fluoroquinolone like levofloxacin has the additional benefit of high prostate gland penetration. Recurrence and relapse are commonly seen in the elderly, so proper follow-up must be arranged.[16]

Returning to the case, the patient is prescribed oral levofloxacin, 250 mg per day for 14 days and allowed to take acetaminophen as needed. Given the fever and neurological symptoms, however, the patient is considered at risk of developing sepsis, so it is decided with the wife and daughter's consent that it would be most prudent to admit the patient to the medicine service.

The next day, the patient's serum lactate remains unremarkable and repeat measurement of his vitals – particularly heart rate and O_2 saturation – return normal findings. He is cooperative and much more aware of his situation, correctly providing his name, the approximate date and the fact that he was in a hospital.[18] Satisfied with the above improvements, the physician discharges the patient and asks the wife and daughter to help fill and administer the remainder of the prescription. They are also instructed to bring the patient to see his family doctor in one week to ensure clearance of the microorganism, confirm relief of neurological symptoms and consider management of incontinence, if it becomes chronic. Referral to a urologist is deemed unnecessary unless further complications occur.

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Diagnosing in the dark: atypical proteinuria etiology

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A zebra is a member of the species of African equids, of the horse family, whose appearance is defined by striking black and white stripes. These animals are rarely seen outside of their native continent, except for their requisite presence in zoos, menageries, and circuses. When we think of something that is common, a zebra may define the direct antithesis to our notion of commonality. Likewise, a zebra patient is, for a physician, a peculiar blend of an exciting presentation and a frustrating diagnosis. The helpful adage "common things are common" can be summarily thrown out of the nearest window when dealing with the contents of the Zebra Files.

Our case begins with an 80 year old gentleman presenting to his primary care physician with an acute history of leg swelling and urinary frequency over the past three weeks. An evaluation of the present complaint determined that he was also experiencing a reduced appetite, nausea and vomiting. On examination, the man's blood pressure was 138/78, and the lower extremities demonstrated the features of pitting edema. Investigations were ordered, and returned as follows: blood urea nitrogen (BUN) of 7.3 mmol/L (normal range 2.9 – 8.6 mmol/L), serum creatinine (Cr) of 457.6 umol/L (normal range 53 – 115 umol/L), and a serum albumin level of 25 g/L (normal range 35 - 50 g/L). Urinalysis was performed, which detected the presence of protein (graded as a 3+) as well as glucose in the urine, with no remarkable microscopic findings.[1] With these results and the clinical picture revealed, we can begin to hypothesize.

The finding of pitting edema on physical exam suggests an accumulation of fluid in the interstitial space of body tissues. Fluid typically pools in dependent areas of the body like the legs and feet.[2] This is reflected in our patient, who had noticed an abnormal swelling of his lower limbs. Pitting edema is a sign of volume overload in patients, which results in excess fluid seeping out of the vasculature into the interstitial space of body tissues. There are several mechanisms by which this volume overload phenomenon can occur. For the sake of brevity, heart failure, liver diseases such as cirrhosis, renal sodium retention, nephrotic syndrome, drug-induced, and idiopathic edema are all potential culprits, especially in an individual of advanced age.[3] Differentiating between these etiologies is critical in order to proceed.

Building on our understanding of this patient's volume status, we can examine the results of the initial investigations. Both urea and creatinine were found to be elevated, which indicate impairment of renal function. The key to the picture here is the urinalysis test. The significant presence of protein in the urine, classified in this case as proteinuria of 3 out of a possible 4 degree of severity, should not be seen in a healthy person and is an indicator of disease.

A differential diagnosis for heavy proteinuria would include glomerular causes such as glomerulonephritis, , diabetic glomerulosclerosis, systemic lupus erythematosus, amyloidosis, and vasculitis. Other causes may include, monoclonal proteinuria, multiple myeloma, lymphoma, or other neoplasia.[4] Renal function is dependent upon filtration in the glomerular unit, resulting in the removal of wastes and the retention of blood cells and proteins. Failure to retain proteins suggests damage to the glomerulus, the filtration unit of the kidney. The absence of blood in the urine, or hematuria, is also helpful. Heavy proteinuria without hematuria falls into one category of renal disease (nephrotic), while the combination is indicative of a different type of pathology (nephritic).[5] The measurement of a low albumin in the investigation of this patient is reflective of the heavy proteinuria.

The patient was referred by his primary care physician to a nephrology clinic for further evaluation. Repeat urinalysis was performed. A 24 hour urine collection for protein was performed, which is more helpful for evaluating the amount of proteinuria than a dipstick urinalysis. The patient was losing 20.7 g of protein over a 24 hour period in his urine. This more focused analysis returned another curious result; in addition to the previously detected proteinuria, trace blood also appeared in the urine. Microscopic analysis identified 10-20 red blood cells per magnification field, with some granular casts.[1] The patient has now demonstrated some degree of hematuria observed in the setting of heavy proteinuria.

The finding of hematuria shifts the diagnostic focus away from a nephrotic syndrome, which is categorically limited to protein wasting in the urine, and usually not blood. Glomerulonephritis is an inflammatory process defined by the presence of red blood cell casts or dysmorphic red blood cells in urine, moderate proteinuria, hypertension, and renal failure.[6] Causes of the nephritic syndrome all relate to various defective autoimmune processes; damage from these circulating factors occurs progressively as these factors accumulate during glomerular filtration. The underlying cause of the glomerulonephritis can be determined by serological tests for these autoimmune factors.

Naturally, in our "Zebra" patient, the usual suspects in the nephritic syndrome (anti-nuclear antibodies, ANCA and anti-GBM antibodies, cryoglobulins, Hep C antibody, ASO titres) turned up negative. However, two proteins (C3 and C4) were found to be abnormally low.[1] These are normally involved in the complement cascade vital to the body's immune response.

A renal biopsy was performed to determine the glomerular pathology. Light microscopic evaluation showed classic characteristics of a membranoproliferative glomerulonephritis, with formation of pathological crescents in 50% of glomeruli. A Congo red stain was performed on the biopsy sample; it returned with a negative result, ruling out renal amyloidosis.[1] After a circuitous diagnostic route, the electron microscopy and immunofluorescence on the kidney biopsy specimen did provide an

answer. The architecture of the glomerular basement membrane was being disrupted by randomly arranged fibrillary deposits. Final diagnosis was determined: fibrillary glomerulonephritis with crescent formation, in the presence of hypocomplementemia.

Fibrillary glomerulonephritis is an uncommon disease of the glomerulus leading to renal dysfunction.[7] This dysfunction is caused by a buildup of randomly arranged fibrillar deposits in the glomerular base membrane and mesangium.[8] The disease was first distinguished in 1977 from amyloidosis on the basis that congo red stains, which stain amyloid fibers, were negative in several patient's kidney biopsies.[1] Fibrillary glomerulonephritis has been associated with different malignancies, monoclonal gammopathies, and autoimmune disorders.[7] Despite the thorough characterization of fibrillary glomerulonephritis, the pathology of the disorder is not fully understood although it is known that the fibrillary deposits are derived from immunoglobulins.[9]

Crescents formation, as seen in our "zebra" patient, is seen in approximately 20% of cases of fibrillary glomerulonephritis. Crescents result from a nonspecific response to severe injury of the glomerular capillary wall. These crescents can involve anywhere from 10% to 80% of the glomerulus.[1] Since crescents result from a nonspecific response, they can be seen in any type of severe glomerular disease.

Although fibrillary glomerulonephritis is not generally considered a rare disease, as it is present in approximately 1% of kidney biopsies, the added complication of hypocomplementemia has only been reported on one other occasion in the literature.[7] Hypocomplentemia can refer to low levels of the molecular mediators of complement; in our "zebra" patient it refers to the decreased amount of C3 and C4.

The treatment of fibrillary glomerulonephritis with crescent formation and hypocomplementemia has not been well established due to the rarity of the condition. Unfortunately, many of the treatment options for other types of glomerulonephritis, such as steroids or cytotoxic agents, are ineffective on fibrillary glomerulonephritis.[7] Conservative use of angiotensin inhibition is often used to control blood pressure and slow the progress of the disease.[10] Some of the therapies that have been attempted to some success involve the use of glucocorticoids, prednisone, cytotoxic agents such as cyclophosphamide, and rituximab.[11]

The prognosis for patients with fibrillary glomerulonephritis is often grave due to the dearth of treatment options. The expected time course can be estimated at the time of a renal biopsy by different histological features seen under light microscopy.[12] Approximately 50% of patients will progress to end-stage renal disease within two to six years. Among the remaining patients, only 10% achieve complete or partial remission while 40% have progressive renal disease.[10] With this outlook, our patient may have become one of the growing numbers of patients who are dependent on renal dialysis therapy, a difficult reality that defines the medical care of so many elderly patients.

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The barriers surrounding hemodialysis for patients with ESRD: improving access since 1945

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Hemodialysis is one option for renal replacement therapy in people with End Stage Renal Disease (ESRD). It is required when a person's kidneys are unable to complete their normal function, that of maintaining the normal intracellular and extracellular fluid environment within the body.[1] It entails removing excess fluid, as well as wastes such as urea, while replacing necessary substances such as bicarbonate.[1] In this article, we present some of the barriers surrounding the implementation of dialysis for patients and explore how some of these barriers were overcome.

EARLY DEVELOPMENT AND IMPLEMENTATION OF HEMODIALYSIS

The first successful use of hemodialysis occurred in the Netherlands in 1945 by Dr Willem J. Kolff with a machine dubbed the "artificial kidney."[2] A 67-year-old woman suffering from acute kidney injury was nearly anuric, but with 11.5 hours of dialysis, her blood urea nitrogen and serum potassium levels dropped and she eventually made a full recovery. Dialysis, still experimental then, was reserved, as in this case, for failures of conventional treatment.[2] Interestingly, a Canadian surgeon, Dr. Gordon Murray, also invented a hemodialysis machine around the same time as Dr. Kolff.[3] In 1946, he successfully dialyzed a woman in a uremic coma at Toronto General Hospital. Despite these successes, hemodialysis was initially met with concern from physicians regarding safety and efficacy, especially since treatment course was determined largely by trial-and-error and few people were trained to operate the machine.[3,4] However, throughout the 1950's, hemodialysis gained popularity and improvements and modifications were made to facilitate treatment and improve outcomes.[5] It was indicated primarily for patients with acute kidney injury who only needed to be dialyzed temporarily rather than for ESRD as it was difficult to maintain vascular access for repeated dialysis to take place.[5] This problem was resolved in 1960 when Dr. Belding H. Scribner and colleagues introduced an arteriovenous shunt, which kept the radial artery and forearm vein in the arm of the patient connected using Teflon tubing.[6] This shunt remained on the patient to maintain vascular access, facilitating connection with the hemodialyzer whenever dialysis was needed.[6]

ONCE HEMODIALYSIS BECAME AVAILABLE TO THOSE WITH ESRD, WHO RECEIVED CARE?

The Scribner shunt made hemodialysis a viable option for ESRD. In 1962, Dr. Scribner opened the world's first outpatient dialysis centre in Seattle.[7] The Seattle Artificial Kidney Centre consisted of only three sets of dialysis equipment with limited staff. Thus, the centre formed two committees to determine which patients were best suited for hemodialysis. The first consisted of nephrologists who ensured patients met stringent medical criteria. The second, the Admissions and Policy Committee, consisted of two physicians, a Christian minister, lawyer, housewife, businessman, and labour leader. It was also nicknamed "the God committee" as its role was to assess the "relative worth" of a candidate to their family and to society at large and chose which patients would survive and which would die from their disease.[7,8] Choices were allowed to be guided by each member's conscience and patients could be evaluated on marital status, occupation, income, education, emotional stability, future potential, gender, and age.[9] Successful candidates were usually those who were hard-working, had many children, were actively involved in church and community affairs, but had few monetary savings such that if they died, the state would have to support the family. As a result, the decisions of the Committee were largely biased towards White, Protestant, middle-class men.[9] Committee members agonized over these difficult decisions and critics felt that determining "social worth" was unethical and suggested that decision-making be based on a method that does not permit the comparison of social worth among individuals, such as choosing by lottery.[7,10] Fortunately, such committees became unnecessary as hemodialysis became more widely available. In 1972, U.S. Congress agreed to provide dialysis in end-stage renal disease for those who could not afford it.[9]

The initial situation in Canada is not unlike that in the United States. Prior to the implementation of the 1966 Medical Care Act, regular dialysis treatments were only offered in a few hospitals due to prohibitive costs.[11] Again, the question of who would receive treatment and how such allocations would be determined posed a dilemma for physicians and policy-makers. Selection committees regulated who received dialysis, based on criteria such as age, the stage of renal disease, absence of other comorbidities, and suitability for kidney transplantation. It was the death of a young man from kidney disease in Montreal that precipitated the creation of the charitable Kidney Foundation of Canada in 1964, dedicated to advocacy, research, and support for Canadians with renal disease. Eventually, under Medicare, the cost of dialysis was fully covered, allowing patients with renal disease access to previously unattainable life-saving care.[11] Advocacy for hemodialysis has saved many lives. In 2009, 22,310 Canadians with ESRD were being treated with dialysis.[12] Although it is known that renal transplantation is the best treatment for ESRD, the number of kidneys available for transplant is not increasing as sharply as diagnoses of ESRD and demand for hemodialysis is expected to increase in the future.[12]

DEVELOPMENT OF HOME DIALYSIS

Even with improved access, hemodialysis, although life-saving, is very time-consuming, invasive, and may negatively impact quality of life.[13] One aspect of initial treatment was that most patients needed to travel to a hospital and dedicate several hours a week to being dialyzed. A method that circumvents this necessity, promoted in Canada by Dr. Robert Uldall and Dr. Andreas Pierratos at the University of Toronto in 1993, is home hemodialysis. This method allows patients to perform dialysis at

home during sleep for most, if not all, nights of the week.[14] Although patients must be trained, home dialysis has been associated with improved quality of life and a higher cost utility compared to traditional in-center hemodialysis.[15] While home dialysis peaked in 1993 at 37.4% of all dialysis in Canada, in 2011 that figure was only 23-24% in Ontario.[12] Home dialysis can be difficult to implement and unsuitable for some patients, but it offers an alternative for patients who would prefer to be treated at home.

EXPANSION OF DIALYSIS TO RURAL SITES

Canada is a vast country and many communities are isolated from large hospital centres containing dialysis units. Many patients are faced with a shortage of dialysis stations in their area and have a limited ability to select their preferred location or schedule for dialysis. Patients living in rural areas may need to make hours-long drives to the nearest hospital, a heavy burden in vulnerable populations such as the elderly and disabled.[16] A delivery model proven to be safe and effective in Ontario is the satellite model, in which rural satellite sites are paired with a larger centre or "hub" to ensure that while patients may receive hemodialysis in a rural setting, they are still granted access to an experienced nephrology team.[17] An example of a satellite dialysis unit can be found in Goderich, Ontario, a town of 8,000 residents about an hour north of London, Ontario. Opening in 2001 as a satellite of the London Health Sciences Centre Renal Program, the facility can accommodate 12 patients per day who would otherwise need to travel to London for hemodialysis.[18] A nephrologist from London visits approximately once a month for patient assessment and adjustment of medications and conference calls are made to discuss patient care on a weekly basis. Although such facilities are primarily for the most stable patients requiring dialysis, they have empowered smaller communities and helped alleviate some of the added difficulties of having ESRD in a rural setting.[18]

CONCLUSIONS

Access to hemodialysis has improved over the years and patients are now empowered with more options for treatment, including home dialysis and access to satellite sites. However, accessibility to treatment remains an issue for chronic kidney disease and ESRD patients. As the prevalence of kidney disease has increased, so has demand for dialysis, from more than 5 900 Canadians on dialysis in 1990 to 22 300 in 2009, an increase from 53% to 59% of all ESRD patients.[12] Furthermore, for many patients, transplantation remains the ultimate goal of treatment. It is known that renal transplantation is generally more effective at treating patients with ESRD and those transplanted report a greater quality of life.[19] In addition, the estimated cost for hemodialysis is approximately $60 000 per year of treatment, per patient, while the cost for a one-time kidney transplant, including annual maintenance medication, is $29 000. The savings are $250 000 over a five year period, especially relevant in light of many recent cuts to healthcare in Ontario.[12]

Due to limited access to donor organs, guidelines have been developed to determine which patients are eligible for kidney transplantation, hearkening back to the early days of hemodialysis. As bioethics has evolved from darker days in Seattle, these criteria are much more transparent and evidence-based. Controversies in organ donation remain, such as whether patients of advanced age or cognitive impairment are treated fairly within the system.[20] By advocating for patients to sign donor cards and express their wishes to family and friends, ensuring that all patients who may benefit from transplantation are assessed and added to waiting lists, we can play a role in ensuring that access to hemodialysis remains widespread, and open to newly diagnosed patients and those ineligible for transplant.

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