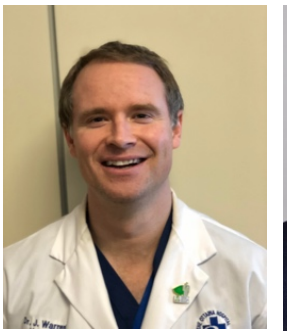
Transplantation and Surgery: A Discussion on the Current and Future Direction of Renal Transplantation


Dr. Warren


Dr. Skinner

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ABSTRACT

Dr. Jeff Warren, MD, FRCPC, is an associate professor at the University of Ottawa within the Department of Surgery, Division of Urology. He has been a staff Urologist since 2009 and obtained his fellowship in multi-organ transplants, including kidneys and pancreases, from the University of Western Ontario. He received his MD from the University of Ottawa in 2002 and also completed his residency at the University of Ottawa in 2007. He is currently the head of surgical foundations for all surgical residency programs at the University of Ottawa. His clinical interests are in kidney transplantation surgery, minimally invasive surgery, and medical education.

Dr. Tom Skinner, MD, FRCPC, is a transplant fellow at the University of Ottawa within the Department of Surgery, Division of Urology. He received his MD from Dalhousie University in 2012 and completed his Urology residency at Queen's University in 2017. He has a BSc. from the University of British Columbia and a MSc. from McGill University. His clinical interests are in minimally invasive surgery, renal transplantation, surgical education, and healthcare economics. During this interview, Dr. Skinner and Dr. Warren discuss the current state of transplant surgery, the biggest challenges to transplanting patients, and the future of the specialty. They also discuss robotic surgery and the Spanish model for organ donation.

RÉSUMÉ

Dr Jeff Warren, MD, FRCPC, est professeur agrégé à l'Université d'Ottawa au Département de chirurgie, Division d'urologie. Il est urologue personnel depuis 2009 et a obtenu son fellowship en greffe de plusieurs organes, y compris les reins et le pancréas, à l'Université Western Ontario. Il a obtenu son doctorat en médecine de l'Université d'Ottawa en 2002 et a complété sa résidence à l'Université d'Ottawa en 2007. Il est actuellement responsable des fondations chirurgicales pour tous les programmes de résidence en chirurgie de l'Université d'Ottawa. Ses intérêts cliniques portent sur la chirurgie de transplantation rénale, la chirurgie mini-invasive et l'éducation médicale.

Dr Tom Skinner, MD, FRCPC, est boursier en transplantation à l'Université d'Ottawa au Département de chirurgie, Division d'urologie. Il a obtenu son diplôme de médecine de l'Université Dalhousie en 2012 et a complété sa résidence en urologie à l'Université Queen's en 2017. Il détient un baccalauréat en sciences de l'Université de la Colombie-Britannique et une maîtrise de l'Université McGill. Ses intérêts cliniques portent sur la chirurgie mini-invasive, la transplantation rénale, l'éducation chirurgicale et l'économie de la santé. Au cours de cette entrevue, Dr Skinner et Dr Warren discutent de l'état actuel de la chirurgie de transplantation, des plus grands défis pour la transplantation des patients et de l'avenir de la spécialité. Ils discutent également de la chirurgie robotique et du modèle espagnol pour le don d'organes.

Tell us a little about your background in Urology, and what got you interested in transplant surgery?

Dr. Skinner: I did my medical training at Dalhousie University in Halifax, after which I did my Urology residency at Queen's University in Kingston. I got interested in Urology by the end of my second year of medical school and did some electives in Kingston and ended up matching there. In my second year of residency, I came here to Ottawa and did a transplant rotation with Dr. Warren. That's where I became interested in transplantation. I had some exposure to transplantation prior to that as an elective student at Dalhousie and it was on my radar, but I

Keywords: Transplantation; Urology; Surgery; Robotic Surgery

didn't know much about transplantation until I came here to Ottawa. At that tme, they didn't have a transplant fellowship program but they created one just before I finished residency, so I applied and have been here since July.

Dr. Warren: My history is pretty similar. I did my undergraduate degree in life sciences and immunology at Queen's University and did medical school at the University of Ottawa. I also did my residency at the University of Ottawa. I had a bit of a background in immunology, and I really enjoyed my nephrology rotation when I was a junior resident. A lot of these things where people end up with ultimate career paths, I think, are more fortuitous than anything. The timing was such that I had an interest and aptitude in transplants and there was a transplant position open in Ottawa when I was a senior. So I went down to Western University for two years and did a fellowship in transplant surgery where I was doing transplants of kidneys, pancreases and a bit of liver as well. I came back to Ottawa in 2009 and have been on staff since. I have a varied urology practice, but my predominant interest and academic focus is on kidney transplants.

What has been the biggest change you noticed since you first started with respect to transplant surgery?

Dr. Warren: I would say in the last ten years, since I've finished up my training and come back to Ottawa, what has changed in Ontario is the sheer number of transplants that we're doing. We're getting more people off dialysis that are candidates for transplants than ever before. With the aging population and obesity crisis, the demographic of patients that we're transplanting has changed. They all tend to be a bit older and more obese, and we are stretching the envelope with acceptability on both of those fronts. Also, something called donation after cardio-circulatory death (or DCD) and domino live chain programs have also improved donor numbers throughout Canada and the United States, and certainly in Ontario, where we are the leaders across the country. So there actually has been a lot of change in the last 10-12 years since I've been involved. Predominantly all those changes are geared towards increasing the number of suitable kidneys that can be transplanted in order to meet the growing demand.

Can you tell us about the different types of donors? What method of donation has the highest success rate?

Dr. Skinner: There are basically three main types of donors. Elective donors are most often a relative or loved one of someone who needs a kidney that come forward. We occasionally have altruistic donors that just hear about kidney donation in the media and decide they want to give a kidney up. These individuals are screened heavily, and if they are deemed to be safely able to proceed with a kidney donation and live with a solitary kidney, they can choose to donate their kidney. Our screening process is extensive for them.

The next tier of donation would be cadaveric donors, and those are broken up into two different categories. Until 2006, they were all NDD, or neurological determination of death. If someone has had a stroke or head injury and they are deemed to have reached the criteria for brain death, usually determined by a neurologist or intensivist, then they can become a candidate to donate their organs. These are considered the highest quality of cadaveric organs, as the heart continues to pump up until the organs are harvested in the operating room.

In 2006, we started doing DCD donation in Canada, which is donation after circulatory death. Those are patients that still typically have some sort of traumatic or head injury, but they don't meet the criteria for brain death and are also unable to go home and have a meaningful life off of life support. They are the second tier of cadaveric donors. Generally, for DCD donation, they typically withdraw life support in the ICU while the surgical team is waiting in an operating room, and the donor is brought in once their vital signs are absent.

What are your thoughts about the Spanish model of transplantation where there is presumed consent unless an individual opts out? Do you see our society going in that direction?

Dr. Warren: That's a very good thought, and very interesting and tmely. Spain, Belgium and the Netherlands are actually the three countries that have adopted an opt-out strategy for organ donation. And certainly I don't think there's any argument that it increases the number of viable donors, just based on the informed consent process. I think it's very difficult from a legal and cultural perspective to implement similar laws in a country like Canada that is very multicultural. Part of the reason is that there are lots of different faiths throughout the world and there are examples where it is not deemed appropriate for patients to donate their organs after death because they may be needed in the next life. There are a few Asian cultures, the Japanese

for example, where the vast majority do not prescribe to organ donation after death. Also, donation laws and how they are handled in Canada are based on a province-to-province basis. At the national level, the Canadian Society of Transplantation has looked at this for the past 10-15 years and it really is a hot topic every year. We often get people from Spain, the Netherlands, and Belgium to come talk about their experiences where you hear some pretty compelling stories. To introduce federal legislation, I think, would be very challenging.

In Spain, they also attempt to preserve organs roadside by paramedics. Do you think that can be implemented in trauma cases?

Dr. Warren: Yes, we have been talking about that. This is a different issue. In countries where they practice this at the scene, the goal is to resuscitate the patient. The paramedics do the resuscitative efforts, and then after the paramedic team thinks its futile, they call the physician at their hospital to tell the story and ask whether or not they get permission to declare death and to cannulate the organs. Once again, the world experience is in Spain with this practice, and part of the reason is because of the informed consent laws there. They are able to do that with minimal ethical implications. It has had a positive impact on the number of organs that are transplanted, not just kidney, but also livers and lungs.

There is talk about doing this in Canada with something called the Maastricht criteria (1), which is where the criteria for donation after circulatory death came from. These would involve what are called uncontrolled DCDs. There is concern about the viability of the organs, but there are certainly some good outcomes in case series from Spain and other countries that have similar practices. That is something that may be a possibility in Canada because you're not taking the organs, you're just preserving the body. It doesn't mean you're going to use those organs for donation, but it gives you tme to contact the families and find out what the patient's wishes were. I think from an ethical perspective and from a legal perspective, that would be the next step. It has not been practiced yet and part of the reason is that most transplant surgeons and physicians are worried about the quality of the organs. Some case series report unwitnessed cardiac arrest, in which case you have the question of whether the organs have been nonviable or ischemic for too long. In countries like Spain, that are very aggressive with their organ donation, it's usually with a witnessed cardiac arrest outside of a hospital. In that situation, at least you have a tmeline for how much ischemia has been there.

Is warm ischemia tme one of the most important markers of kidney viability from the surgical point of view?

Dr. Skinner: Yes. With cadaveric donors, that is the difficult hurdle we have to overcome. It plays a role in organ transplantation because there's always going to be warm ischemia tme during the implantation phase when you're sewing the kidney in. We usually talk about it more in the context of the donation side. In deceased donors it's important because it's an independent marker of both delayed graft function (DGF) and long-term kidney success rates. But as a group, you can group them into high and low warm ischemia tmes. NDD donors, for example, have extremely low warm ischemia tmes and that's why they tend to be of superior quality.

However, with DCD donors, the battle you are fighting is from the tme that their vital signs are absent, they have to be transported to the operating room, placed on the operating table, and you still have to cut down and find the vessels, cannulate them, and flush. There is always a 5-10 minute delay that's unavoidable and that is the primary reason why those organs are of inferior quality. DCD's have much higher delayed graft function rates and renal failure rates.

Back in 1989, it had been reported that approximately 20% of kidneys transplanted were not functional past their first year (2). The number has now decreased to as little as 5% and is often related to rejection of the donor organ. Could you explain how future therapies will attempt to combat this issue?

Dr. Warren: That's a good question. The one-year endpoint has a lot to do with the kidneys that we lose for immunological reasons and acute rejection. This is difficult to get around because it encompasses not just rejection from a graft perspective but various native kidney diseases as well. The classic example are people with a primary glomerulopathy, like focal segmental glomerulosclerosis (FSGS) in young people. They tend to be anywhere between 3-10% of the transplants that we do in Canada. A lot of those unfortunate young recipients are going to lose their newly transplanted kidneys because of recurrence of disease. This is very difficult to control and an argument can be made that some of these people shouldn't be transplanted in the first place because the prognosis is so poor.

The main reason that the one-year rates have improved from 20% graft loss down to about 5% is because of the improvement and aggressiveness of immunosuppression, with newer calcineurin inhibitors that work better and especially with the advent of newer anti-proliferatives. The classic example is mycophenolate (which is also known as CellCept), and these have really diminished the risk of acute rejection. The loss of kidneys from acute rejection in the first year has decreased because of better pharmacology. The surgery itself has not changed in the last 30-40 years. I do think we are a bit more efficient in minimizing both the warm ischemia tme and the cold ischemia tme. Whether or not the recent use of Lifeport perfusion pumps is going to extrapolate long term and lead to better kidney functioning at one year I think remains to be seen. But I really don't think you're going to get much more improvement over 5% graft loss unless we completely revamped the whole idea of transplantation, such as growing kidneys that are specific for recipients and therefore don't require immunosuppression.

How far do you think we are from that?

Dr. Warren: Well, I'm 41 now and plan to practice until I'm about 60 or thereabouts. Whether or not it happens in my career, I think, is difficult to tell. It is kind of like any new technology, things tend to explode. They go from 0 to 60 pretty quickly. For example, I didn't have a cellphone when I was a resident, and that wasn't too long ago. I got a cell phone my second last year of residency, which sounds like a long tme ago but it was 2005. There is the possibility for artificial kidneys but there are certainly immunological challenges to overcome. Dr. Tony Atala, who's an expert in regenerative medicine and happens to be a urologist, is already growing organs in scaffolds. It's a matter of populating those organs with cells that are viable, and then making them HLA compatible or completely inert with the recipient.

There's the possibility that this may replace the entire role of surgery and transplantation, where you can actually just inject cells that will do a renal-like function somewhere else in the body. Now, the problem with any organ that you're going to replace that has an excretive function, is that you still have to get rid of the waste somehow. The kidneys and liver are good examples of this. In cardiac transplants however, it's a possibility where you might be growing hearts in petri dishes. There's already a physician down in Texas that has been growing hearts that have no antigen on them and the question is whether or not they are going to be feasible. I think that we will actually do this with hearts before we do it with kidneys or livers. But in the next 10-15 years, probably not.

What is robot-assisted surgery? Who is doing the surgery? Is there artificial intelligence involved?

Dr. Skinner: Robotic surgery is an extension of laparoscopy. Laparoscopy is a form of surgery where you inflate the body cavity that you're working in with an inert gas like carbon dioxide and you work in that space with long instruments through small ports so that your incisions are much smaller. Laparoscopy has become the standard of care in most surgeries. General surgery, gynecological surgery and urology are doing at least some of their surgeries laparoscopically. Robotic surgery is just an extension of that where there are laparoscopic ports inserted into a cavity filled with an inert gas, but the surgeon is not directly connected to these instruments. So they are sitting at a console and are directly manipulating the robot's arms. There is no artificial intelligence where the robot is doing parts of the procedure on its own, but it can assist the surgeon by reducing tremor, or by moving a very small instrument in a confined space with much more degrees of freedom than the human hand can do in the same space. But it is still always under the control of a surgeon at the console.

What is the biggest challenge you see within kidney transplantation in the future?

Dr. Skinner: The biggest hurdle for transplantation is getting everyone transplanted. There's more people with end stage renal disease than there are kidneys available for them. Increasing donors by any means (live donors, deceased donors, and extended criteria donors) to get people transplanted, or improving other forms of renal replacement therapy will help. But we know that mortality rates on dialysis are very high, and quality of life (on dialysis) is very low. Kidney transplant is superior in essentially all realms, including financially, so, we need to find ways to transplant more people, and I think that's the biggest thing to overcome.

Dr. Warren: I think that the holy grail for transplantation has always been tolerance. Being able to transplant an organ from two people that are not genetically identical without having the morbidity, side effects, complications, and the long-term sequelae of the immunosuppressive medications. So while

there are lifesaving medications, they're not perfect. There's a lot of side effects, risk of long term cardiovascular toxicity, other end organ damage, infections and malignancy. So tolerance is an immunological challenge of transplantation, and if you think about what we talked about a few questions ago about being able to grow kidneys in a petri dish, so to speak, you may be able to bypass all of the problems of tolerance because you can make the tissue genetically inert. It's like putting in a titanium clip, but it actually functions like an organ and by definition then will be tolerant because there is no antigen. So I think that is the holy grail or the ultimate goal of the transplantation. Whether or not that's a reality in the next 20-30 years remains to be seen.

Is Xenotransplantation, the use of organs from different species, a possibility? What are some barriers?

Dr. Warren: We are moving away from that direction. There has not been much interest in that for the past 10-12 years. 20-30 years ago there was an interest because a supply of organs from different species would not be a problem; however, if you look at experimental models, xenotransplantation due to immunological mechanisms between species is not a good idea. It leads to very acute rejection and intolerance within the host. The only exception to this is heart valves which can be taken from bovine or porcine sources. These are tissues that are inert and not very antigenic, but if you are trying to transplant a visceral organ like a liver, kidney, or heart it will not work. Human-to-human transplants are still not perfect, but between species is not viable.

What do you enjoy most about surgery and what advice would you give to students considering transplantation surgery?

Dr. Skinner: What drew me to surgery was in part the people. Obviously, there is a technical aspect to surgery that I really enjoy but there is also a great deal of comradery within the field which definitely played a role in my decision to pursue it. In Urology, there is a large variety of procedures and interventions that you can do with a good balance between surgery and medicine. We also have long term follow up for some patients, which allows you to get to know them over tme. Transplantation is one of the more technical procedures within the field, and one of the procedures that is immediately gratifying. When you take a kidney off clamp and see it change color and start producing urine, it's a very satisfying moment. Urologists happen to do interventions that have significant impacts on quality of life, which is very rewarding. Just seeing people go through dialysis with end stage renal disease and observing the improvement in quality of life made by a renal transplant is amazing.

My advice for medical students would be to explore different specialities and see how you fit with the people who work in that specialty. Your preceptors will become your future colleagues, which can be difficult to appreciate early on but is important to consider. You should try and see what the more common interventions in any speciality are and ask yourself if you could do that for the rest of your life. Again, not easy to do early on but something to consider. My advice for medical students when on the wards and on electives would be to have a positive attitude, show interest, and be professional. If you are considering Urology or surgery in general, research helps but isn't mandatory. It can be difficult with all the stressors of medical school but I would encourage you to continue to maintain your hobbies and interests outside of medicine. Finally, just remember there is no cookie cutter path for a career in surgery, everyone takes their own route, as will you!

Dr. Warren: I would echo all of Tom's comments about that. One thing that I think is unique about transplant surgery in particular is it's one of the few exceptions in surgery where you get to put something into a patient. Almost everything we do in surgery is taking something bad out of a patient, except this is the instance where you get to put something good in.

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