A Message from the Activity Director

On behalf of the Continuing Medical Education Office at the American University of Beirut and the Cleveland Clinic Center for Continuing Education, it gives me great pleasure to welcome you at the Kidney Transplantation Course from November 11 to 12, 2010 at the Golden Tulip Serenada Hotel - Beirut, Lebanon.

The two day course targets opinion leaders and pioneers among Middle Eastern physicians, nurses and health workers caring for patients with end stage renal disease who require or have undergone kidney transplant.

The course will identify challenges in meeting the needs of the Middle East population for transplantation, describe current and future immunosuppressive therapy used in kidney transplant, distinguish advantages and disadvantages of laparoscopic donor nephrectomy, describe management of common complications including infectious and cardiovascular diseases and discuss challenges in organ donation and allocation in the Middle Eastern countries.

I look forward to seeing you.

Best regards,
Mohamed H. Sayegh, MD
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Raja N. Khuri Dean of the Faculty of Medicine and the Medical Center
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Activity Directors

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Dr. Antoine Stephan  
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General Information
General Information and Accreditation

Program Overview
This is a two day program targeting opinion leaders and pioneers among Middle Eastern physicians, nurses and health workers caring for patients with end stage renal disease who require or have undergone kidney transplant.

Objectives
After completing this activity, the participant will be able to do the following:
1. Identify challenges in meeting the needs of the Middle East population for transplant
2. Describe current and future immunosuppressive therapy used in kidney transplant
3. Distinguish advantages and disadvantages of laparoscopic donor nephrectomy
4. Describe management of common complications including infectious and cardiovascular disease.
5. Discuss challenges in organ donation and allocation in the Middle Eastern countries

Venue
The course is held at the Golden Tulip Serenada Hotel, Beirut, Lebanon from 11 till 12 November, 2010.

Accreditation Statement
This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of The Cleveland Clinic Foundation Center for Continuing Education and American University of Beirut Medical Center. The Cleveland Clinic Foundation Center for Continuing Education is accredited by the ACCME to provide continuing medical education for physicians.

The Cleveland Clinic Foundation Center for Continuing Education designates this educational activity for a maximum of 9 AMA PRA Category 1 Credits™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Participants claiming CME credit from this activity may submit the credit hours to the American Osteopathic Association Council on Continuing Medical Education for Category 2 credit.

Lebanese Order of Physicians Statement
The Kidney Transplant Course also complies with the Lebanese Order of Physicians Continuing Medical Education guidelines.

Grantor Acknowledgment
The Cleveland Clinic Foundation Center for Continuing Education and the American University of Beirut Medical Center acknowledge an educational grant for support of this activity from:

Novartis Pharma Services AG
Target Audience
This annual scientific meeting has been designed primarily for physicians in the Kidney Transplant field.

Faculty Disclosure
In accordance with the Standards for Commercial Support issued by the Accreditation Council for Continuing Medical Education (ACCME), The Cleveland Clinic Foundation Center for Continuing Education requires resolution of all faculty conflicts of interest to ensure CME activities are free of commercial bias.

The following faculty have indicated that they may have a relationship, which in the context of their presentation(s), could be perceived as a potential conflict of interest:

- Flavio Vincenti, MD
  - Bristol Myers Squibb Research Support
  - Novartis Pharmaceuticals Research Support
  - Genentech Research Support
  - Astellas Pharma Research Support
  - Pfizer Research Support
  - Amgen Research Support

The following faculty have indicated they have no relationship which, in the context of their presentation(s), could be perceived as a potential conflict of interest:

- George Abi Saad, MD
- Lina Assad, MD
- Antoine Barbari, MD
- Ghassan Hamadeh, MD
- Georges Juvelekian, MD
- Mohammad Khalifeh, MD
- Riad Khalifeh, MD
- Raja Khauli, MD
- Samir Mallat, MD
- Walid Medawar, MD
- Khaled Meshari, MD
- Jacques Mokhbat, MD
- Bjorn Nashan, MD
- Emilio Ramos, MD
- Ibrahim Salti, MD
- Mohamed H. Sayegh, MD
- Antoine Stephan, MD

Disclaimer
The information in this educational activity is provided for general medical education purposes only and is not meant to substitute for the independent medical judgment of a physician relative to diagnostic and treatment options of a specific patient's medical condition. The viewpoints expressed in this CME activity are those of the authors/faculty. They do not represent an endorsement by The Cleveland Clinic Foundation. In no event will The Cleveland Clinic Foundation be liable for any decision made or action taken in reliance upon the information provided through this CME activity.

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Program
Thursday 11 November, 2010

8:00 9:00  Registration

9:00 10:20  Tour of the Medical Center

10:20 10:45  Welcome and Introduction remarks
  Drs.: Ghassan Hamadeh, Mohamed H. Sayegh and Mohammad Khalifeh

Chaired by Dr. Raja Khauli and Dr. Samir Mallat

10:45 11:15  Optimal antibody induction therapy (NON-CME)
  Dr. Bjorn Nashan

11:15 11:45  Current status of immuno suppression in transplant
  Dr. Flavio Vincenti

11:45 12:15  Use of mTOR (mammalian target of rapamycin) in transplantation (NON-CME)
  Dr. Bjorn Nashan

12:15 13:45  LUNCH

13:45 14:15  Surgical complications of transplantation
  Dr. Raja Khauli

14:15 14:45  Non- Infectious complications of transplantation
  Dr. Samir Mallat

14:45 15:15  Metabolic complications of transplantation
  Dr. Ibrahim Salti

15:15 15:45  New biological agents in transplantation
  Dr. Flavio Vincenti

15:45 16:15  COFFEE BREAK

Chaired by Dr. Mohammad Khalifeh and Dr. Antoine Stephan with the participation of
  Dr. Antoine Barbari, Dr. Riad Khalifeh and Dr. Georges Juvelikian

16:15 16:45  Panel Discussion: Challenges in organ donation in the Middle East

  Breaking bad news and obtaining family consent?
  Dr. Antoine Stephan
  On the necessity of limiting and regulating LURD
  Dr. Antoine Barbari
  The importance of intensive reanimation first to save the patient and later to
  salvage the organs
  Dr. Georges Juvelikian

* A five minute question and answer period is included in each of the speaker’s allotted time.
Friday 12 November, 2010

Chaired by Dr. Emilio Ramos and Dr. Walid Medawar

8:30 9:15 Pathology of the kidney transplant, what have we learned
Dr. Lina Assaad

9:15 10:00 Sensitized patients – Problems and Solutions
Dr. Khaled Meshari

10:00 10:30 Chronic allograft rejection
Dr. Mohamed H. Sayegh

10:30 11:00 COFFEE BREAK

11:00 11:30 Infection post transplant
Dr. Jacques Mokhbat

11:30 12:00 Diagnosis and management of polyoma virus infections
Dr. Emilio Ramos

12:00 13:30 LUNCH

Chaired by Drs.: Emilio Ramos, Lina Assaad and Samir Mallat

13:30 15:30 Workshops of case discussions: Unusual cases by participants

15:30 16:00 Feedback

16:00 Adjourn

* A five minute question and answer period is included in each of the speaker’s allotted time.
Abstracts
Surgical Complications of Renal Transplantation

Dr. Raja Khaulil

Surgical complications of renal transplantation have become a rare event with the use of meticulous techniques. Nevertheless, when surgical complications occur, they are devastating and frequently result in graft loss or diminished renal function. The complications are subdivided into 3 categories: 1-Vascular, either arterial or venous, 2-Urological, which comprise urinary leaks and ureteral stenosis, 3-Lymphatic, which include lymphoceles and lymphatic fistulas.

1. **Vascular complications**: these include intimal tears, arterial spasm, arterial thrombosis as well as venous thrombosis and disruption. These are rare complications and occur in less than 1% and can be avoided by careful techniques in harvesting and implantation. Faulty techniques can precipitate early ischemic events of ATN, arterial occlusion, and thrombosis. Inadvertent transaction of segmental arteries is more frequently observed in cadaveric procurement and laparoscopic donor nephrectomy (especially on the right side). Laparoscopically retrieved kidneys have been reported to be a greater vulnerability for arterial spasm, luminal thrombosis, and intimal injury, necessitating modification of the techniques or avoidance of right nephrectomy at some centers. Other difficulties in laparoscopic procurement of the right kidney are the short renal vein which has been implicated by some to cause renal vein thrombosis in early series. This can be prevented by complete mobilization of the renal vein to the caval junction and mobilization of the external iliac vein in the recipient.

2. **Urological complications**: these are mostly ureteral and can be prevented by meticulous ureteral harvesting. They can lead to major complications of urinary leak and ureteral stenosis, resulting in graft loss, morbidity and mortality. Ureteral complications are secondary to ureteral skeletonization and devascularization, ureteral stretching, utilization of an excessively long ureter that is ischemic in its distal segment. Urinomas have been reported in 1-6% of cases and are associated with 30% to 50% of graft loss, clearly unacceptable in this era. Ureteral stenosis occurs during the early period in 1% -5.5% of cases, in the first year and will progressively increase to 10% at 5 years. Early injuries are managed by re-exploration and anastomosis of ureter to the bladder (ureteroneocystostomy) or anastomosis graft renal pelvis to the native ureter (pyeloureterostomy). Late injuries can be managed either by endo-urological techniques including ureteral dilatation and stenting, or by open surgery.

3. **Lymphatic complications**: these include lymphoceles which can occur in 1 to 18 % of transplants. The majority are subclinical and but a few lymphoceles can reach large sizes and become symptomatic necessitating intervention. Most lymphoceles result from the trans-section of the perivascular lymphatics or the Graft renal hilum, and can be avoided by careful coagulation and ligation time of transplantation. The management of symptomatic lymphoceles depends on the presence or absence of infection. The treatment of infected lymphoceles consists of percutaneous drainage and antibiotic therapy. Symptomatic uninfected lymphoceles are treated by laparoscopic internal marsupialization.

Surgical complications of renal transplantation are avoidable by attention to details, exercising meticulous technique, and avoidance of any insult to the ureter or renal vessels. Our center has adopted routine Laparoscopic Donor Nephrectomy has introduced several modifications in the procedure, obviating problems reported in early series. Other modifications in the recipient operation have added to the safety of transplantation.
Non-Infectious complications of transplantation

Dr. Samir Mallat

With the progress made with immunosuppressive therapy, acute rejection episodes decreased and patient’s survival improved. However, non infectious complications are still numerous and will impede on patient’s morbidity and mortality. A better understanding to their pathogenesis has led to a better screening, especially in cardiovascular disease and de novo post transplant diabetes Mellitus. New treatments have been applied toward recurrent glomerular disease and new onset of neoplasia. A better understanding of immunology has also emerged leading to a more “pathogenic” treatment to chronic antibody mediated rejection and graft loss.

Metabolic complications of transplantation

Dr. Ibrahim Salti

Renal transplantation results in a number of metabolic abnormalities the most important of which are:

1. **Lipid abnormalities**, occur in up to 60% of patients. While abnormalities in lipid metabolism are often present before renal transplantation due to the uremic state, after transplantation and recovery of renal function, many lipid disturbances usually persist but show a different profile due to the multiple effects of immunosuppressive drugs on lipid metabolism. These include glucocorticoids and calcineurin inhibitors and Rapamycin all of which result in quantitative and qualitative abnormalities of very low-density, low-density, and high-density lipoproteins.

   Management of post-transplant dyslipidemia is important in order to reduce the high cardiovascular risk of these patients. In addition to dietary measures, statins are effective and relatively safe. Other pharmacological interventions include addition of Ezetimibe or fibrates.

2. **Post-renal transplant diabetes mellitus**: Post-transplant diabetes mellitus is a major problem that endangers patient and graft survival. The incidence of post-transplant diabetes is up to 18% of patients leading to a further increase in their cardio-vascular risk and thus should be closely monitored after transplant and aggressively treated to minimize the risk of complications.

   Development of inpatient hyperglycemia after kidney transplantation in nondiabetic patients significantly increased the risk of new onset diabetes mellitus resulting in a significantly increased risk of cardiovascular events. Other risk factors for the development of new-onset diabetes after transplantation include: age, non-white ethnicity, hepatitis C infection, glucocorticoid therapy for rejection, and chronic immunosuppression with cyclosporine and tacrolimus. The observation that current immunosuppression using tacrolimus is one of the most important single risk factor for the development of new-onset diabetes after transplantation has been made. The pathophysiology of this condition resembles that of type 2 diabetes mellitus. There is conclusive evidence that pretransplantation end-stage renal disease is an insulin-resistant state, and after transplantation, glucocorticoids induce further peripheral insulin insensitivity.
3. **Parathyroid and mineral metabolism after renal transplantation:** Chronic kidney disease is associated with a cascade of events that adversely affect mineral metabolism and lead to renal osteodystrophy. Included in this group are initial phosphate retention, secondary hyperparathyroidism, decreased synthesis of calcitriol, and the accumulation of β2-microglobulin and/or aluminium toxicity.

Successful renal transplantation, by normalizing urinary phosphate and β2-microglobulin excretion and renal calcitriol production, reverses many of these abnormalities in mineral and bone metabolism, including:

A fall in the plasma phosphate concentration to normal, a reduction in plasma PTH levels, a decrease in plasma alkaline phosphatase levels, indicative of less bone resorption, mobilization of soft tissue calcifications, as correction of hyperphosphatemia markedly lowers the calcium-phosphate product.

However, the degree of improvement is frequently incomplete. The primary abnormalities that can persist after transplantation are hyperparathyroidism, aluminium and beta2-microglobulin accumulation, and diabetic bone disease. In addition, osteopenia and osteonecrosis are important causes of long-term morbidity in transplant recipients.

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**New biological agents in transplantation**

*Dr. Flavio Vincenti*

The first decade of the new millennium has been disappointing in transplant therapeutics: no new immunosuppression agents have been approved. Currently, 4 new agents, 2 small molecules (sotrastaurin: a protein kinase C isoforms inhibitor; tasocitinib, a selective Janus kinase inhibitor) are in phase II trials and 2 biologics (belatacept, a second generation CTLA4 Ig and alefacept, a LFA3-IgG1 fusion receptor protein) are in phase II/III clinical trials.

The 2-year results of the phase III trials of belatacept and the phase IIb results with tasocitinib are being presented at this meeting.

A therapeutic area that is likely to experience a dramatic change is the targeting the humoral network: B cells/Plasma cells/HLA antibodies. Novel agents to target B cells include humanized antibodies to CD20 that produce more effective depletion B cells, a humanized antibody to CD22, Atacicept, a fusion receptor protein that neutralized Blys and April and result in B cell depletion and decrease in immunoglobulins and belimumab, a humanized antibody against Blys. Proteasome inhibitors that result in apoptosis of plasma cells are likely to be used more extensively, but their exact role, efficacy and safety need to be evaluated in rigorous trials. The humanized anti-C5 mAb Eculizumab is potentially useful for blocking the injury for DSA and may also have a role potentially to prevent ischemia reperfusion injury. Based on the current pipeline, it is obvious that the next decade will yield better and more focused therapies than the disappointing first decade of this century.
On the necessity of limiting and regulating LURD

Dr. Antoine Barbari

Human organs can be harvested from two main sources: living and cadaveric donors. The preference should go to cadaveric donation since it represents at present the only source of organ for several non-renal solid organ transplantation and is the only modality where there is no risk to the donor. Unfortunately, even in the best developed cadaveric program, only 50% of the need could be barely covered because the demand far exceeds the supply. Living donation, therefore, will have to be seriously considered. This is supported by the fact that the risk for the live donor is minimal and the graft survival is significantly better than cadaveric kidneys regardless of their HLA matching. Moreover, some ethicists and religious scholars from the Middle East region have fewer difficulties with voluntary living donations than with the removal of an organ from a cadaver. Living related donation (LRD) has been limited by the number of willing and valid donors, the high incidence of familial and consanguinity-associated renal diseases and the female donor coercion (especially in our area). Living unrelated donation (LURD) increases donor pool, decreases the chances of coercion if regulated and eliminates the problem of consanguinity. It raises, however, the ethical issues of commercialism, transplant tourism and organ trafficking. It may also endanger if not prevent the development of deceased-donor donation (DDD) program that is badly needed in our area. We propose a series of rules and regulations that are in close agreements with the Amsterdam resolutions and the recent Guiding Principles of the Istanbul Declaration. They have been continuously modified over the last 20 years to try to implement our ideal which is to maximize organ procurement through the promotion and development of a DDD program while regulating LURD through the protection of the interest of the living donor and the prevention of transplant tourism and commercialism and organ trafficking.

Panel Discussion: Challenges in Organ Donation in the Middle East

There can be no transplantation without organs. Dr. Antoine Barbari will discuss why living donors although insufficient, are still needed and Dr. Georges Juvelikian will describe the difficulties in the maintenance of the donated organs.

The importance of intensive reanimation first to save the patient and later to salvage the organs

Dr. Georges Juvelikian

With the worldwide shortage in organs and the limited number of organs that can be provided by a living donor, deceased organ donation is currently the first and major source of organs in the world. A central step in the organ procurement process is the care of the critically ill patient- primarily to save his/ her life, and later to maintain this potential donor until harvesting is complete. Caring for a “brain dead” patient offers its own challenges that intensivists need to be aware of for optimal yield.
Pathology of the kidney transplant, what have we learned

Dr. Lina Assaad

Significant improvements is short-term allograft survival have been accomplished but did not translate into extension in long term function. Therefore late allograft failure is the challenge while the underlying disease processes are mostly elusive.

In 2005, the Banff working group for allograft pathology eliminated the term “chronic allograft nephropathy”, and pathologists have been urged to assign a specific diagnosis instead of using this generic name.

Simultaneously, considerable research efforts (i.e. the Genome Canada Project and Deterioration of Kidney Allograft Function study) were implemented to identify specific causes of renal allograft failure. In 2009, results from these initiatives were presented indicating that antibody-mediated rejection and recurrent/de-novo glomerulonephritis are the major causes of late renal allograft failure.

With new diagnostic tools available, a disease-specific approach in renal allograft damage becomes feasible. This will allow for designing entity-specific trials and establishment of specific treatments, eventually improving long-term allograft function.

Sensitized Patients – Problems and Solutions

Dr. Khaled Meshari

Patients become sensitized after exposure to non-self human leukocyte antigen (HLA) during pregnancy, blood transfusions, and organ transplantation.

It has been estimated that 20 – 30 % of patients awaiting their first renal allograft are sensitized, whereas 77% of patients waiting for repeat transplant are sensitized and 30% of these are highly sensitized (patients with HLA-specific antibodies reactive with > 85% of lymphocyte panel).

These patients, especially the highly sensitized, have the least chance to receive a kidney because most of the randomly performed cross-matches will be positive. Therefore, these patients will continue to accumulate on the waiting lists.

There are three (3) main approaches that can be adopted in order to minimize the phenomenon of sensitization on one hand and maximize the chances of transplanting sensitized patients on the other hand.

The first approach is preventive in nature and it concentrates on minimizing HLA mismatches in the first kidney transplant and on the use of erythropoietin or transfusion with leukocyte-depleted blood for the treatment of anemia in patients with advanced CKD.

The second approach revolves around finding a cross-match negative kidney through national exchange programs (sharing of zero-mismatched kidneys, acceptable mismatch programs, and paired kidney exchange (donation).
The third approach attempts to remove and neutralize the donor-specific HLA antibodies from the serum of these patients before transplantation (desensitization).

We report our experiences in desensitizing highly sensitized patients using a variety of protocols that include: Immunoadsorption, plasmapheresis, VIG, Rituximab, and ATG.

Chronic allograft rejection
Dr. Mohamed H. Sayegh

The most common cause of late allograft failure, excluding death with a functioning graft in the case of kidney transplantation, is a clinicopathologic entity termed chronic rejection, a feature common to all solid organ transplants, including kidney, heart, lung, pancreas and to a lesser extent, liver. Morphological findings associated with this process include progressive narrowing of hollow structures within the allograft, regardless of whether they are vessels (heart and kidney), bronchioles (lung) or ducts (pancreas and liver). Despite extensive research, the precise mechanisms responsible for the characteristic pathological changes seen in chronic rejection remain unclear. Both alloantigen-independent and alloantigen-dependent mechanisms have been shown to be responsible for the development and progression of chronic rejection, although it is clear that the alloimmune response predominates. Alloantigen-independent factors include organ injury secondary to brain death in the donor, ischemia/reperfusion injury, cytomegalovirus (CMV) and other infections, hypertension, hyperlipidemia, cellular senescence, and toxicity of immunosuppressive medications. These factors likely act in concert with the alloimmune response and may not of themselves be sufficient to effect the characteristic changes seen in chronic rejection. Indeed, several lines of clinical and experimental evidence support the critical role of the alloimmune response in initiation and progression of chronic rejection. These include the influence of HLA matching, the impact of acute rejection and under-immunosuppression, and most importantly, in the experimental models, the prevention of chronic rejection when tolerance is induced. New insights into the immunopathogenetic mechanisms of chronic allograft rejection and new approaches to therapy will be discussed.

Diagnosis and management of polyoma virus infections
Dr. Emilio Ramos

Polyomaviruses: BK virus manifests as BKN in immunosuppressed patients; JC virus as PML.

EPIDEMIOLOGY
By age 6, 60-80% of children have antibodies against BK virus. Asymptomatic viruria with BK virus occurs in 0.3% of non-immunosuppressed patients; 3% of pregnant women during the third trimester; 10% of patients with malignancies, mainly lymphoma; and 10% - 45% of renal transplant recipients

CLINICAL MANIFESTATION
The majority of the patients with viruria are asymptomatic; occasionally leukocytes are detected in the urine. However, in approximately 2-10% of these cases, the patient develops BK nephritis, manifested by an increase in serum creatinine in association with interstitial nephritis.
**DIAGNOSIS**

The diagnosis of BK nephritis is made mainly by histological protocol or after graft dysfunction, prompting a kidney biopsy. Other adjunctive tools for diagnosis include cytopathology of the urine, detecting “decoy cells”. Viral particles can also be seen on electron microscopy PCR amplification of the BK virus in blood or urine is also helpful in diagnosis.

**PATHOLOGY**

Polyoma virus renal disease is diagnosed by the observation of tubular viral cytopathic changes in renal biopsy and confirmation by immunohistochemistry, electron microscopy or PCR studies. The differentiation between polyoma virus infection and acute rejection may be difficult.

Drachenberg grades the pathology of BKAN in 3 stages, based on the degree of inflammation and fibrosis. Mannon et al. found similarities in patients with PVAN and AR, including immunohistochemical, and analysis of inflammatory infiltrates. In addition transcription molecules associated with fibrosis were higher in BKAN than AR.

**TREATMENT**

No effective treatment for BK nephritis other than early diagnosis. Judicious decrease in immunosuppression may arrest/progression of the disease.