

Global Scientific Vision With Local Vigilance: Renal Transplantation in Developing Countries

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Context: Renal Transplantation is the most effective treatment for patients with end-stage renal disease, which is fortunately available in the developing countries, even for poor people. Nonetheless, the way forward should be the implementation of advanced science of transplantation, allograft monitoring abilities, knowledge about the epidemiology of renal disease in any specific region, awareness about the influence of ethnic and genetic factors immunosuppressant bioavailability, and post-transplant complications all strongly affecting the patients and allograft survival.

Evidence Acquisitions: In this process we searched mainly in PubMed, Web of Science and Google Scholar data bases for key words of renal allograft monitoring, post-transplant infections, renal/kidney transplantation and Iran. We followed the cross articles to follow our main idea to find a connection between modern advancement in renal allograft monitoring and our practice in developing countries. Another focus was on the special infectious and non-infection complication that do exist in specific region and need specific considerations.

Results: Implementation of modern techniques of immune monitoring, allograft function, awareness about the specific infectious and non-infectious disease in each region improves the quality of renal transplantation.

Conclusions: We need to combine the advance scientific vision with local vigilance to achieve the best outcome in renal allograft recipients

Keywords: Transplantation; Tissue Donors; Antibodies; MicroRNAs

1. Context

Renal transplantation is the most effective treatment for patients with end-stage renal disease. Fortunately, this treatment is available, even for poor people, in developing countries (1); in these countries, however, the way forward should be increasing the quality and expanding the knowledge of transplantation medicine and implementation of advanced technology of allograft monitoring rather than increasing the centers. Better understanding of the epidemiology of renal disease will lead to better management and outcome. Emerging epidemic of diabetes and hypertension are expanding very fast in the Middle East; moreover, special genetic, infectious, and immunologic factors do exist in certain region that need special consideration (1, 2). Some ethnic groups are at increased risk of immunosuppressant complications; therapeutic index for immunosuppressive medicines is narrow and should be in a fine balanced to avoid underdosing or overdosing. In renal transplant recipients, unusual infections are common and might have an unusual pictures. Infections complications not only depend on the state of immunosuppression, but also on the genetic background of the patients (3, 4).

2. Evidence Acquisitions

In this process we searched mainly in PubMed, Web of

Science and Google Scholar data bases for key words of renal allograft monitoring, post-transplant infections, renal/kidney transplantation and Iran. we followed the cross articles to follow our main idea to find a connection between modern advancement in renal allograft monitoring and our practice in developing countries. Another focus was on the special infectious and non-infection complication that do exist in specific region and need specific considerations.

3. Results

3.1. Primary Renal Disease and Genetic Factors

It is very important to have enough knowledge about the underlying renal disease. Early recurrence of mild IgA nephropathy (IgAN) happens in up to 32% of patients within the first year of transplantation; nevertheless, most of the time it is mild and does not associate with lower clinical outcome (5). The phospholipase A2 receptor (PLA2R) antibody is a good marker of primary membranous nephropathy (MN) and its activity and recurrence after transplantation (6). A higher recurrence rate of MN has been observed in recipients of living related donor than in recipients of living unrelated donors. The

role of genetic factors in higher recurrence such as *HLA-DQA1* allele should be studied in different populations (7).

Systemic Lupus erythematosus (SLE) needs special considerations although there are good outcome in SLE patients who have received kidney from living donors (8). Multiple myeloma (MM) is an important cause of renal failure and often presents in various and confusing features. Missing the underlying MM could be a great mistake, particularly when patient is planned for preemptive renal transplantation (9, 10). Combined kidney and bone marrow transplantation without immunosuppression has been reported as a successful modality for patient with MM and renal failure (10). Primary focal segmental glomerulosclerosis (FSGS) often recurs immediately after transplantation. Genetic study of the patients and searching for circulatory permeability factors such as soluble urokinase-type plasminogen activator receptor (SUPAR) are important to understand the underlying pathophysiology and monitoring the recurrence of FSGS (11, 12). It has been reported that the type of dialysis modality does not affect the patient and graft outcome (13, 14); however, hepatitis viruses transmission is higher in patients on hemodialysis while peritoneal dialysis has its own special complications (15, 16). Despite the good result of transplantation in aged population, increased risk of infection and hidden comorbid conditions should be considered in them (17).

3.2. Watching the Allograft

Intrarenal hemodynamic monitoring of the allograft and measurement resistive index are useful and noninvasive methods of monitoring and each transplant center should expand its experiences; moreover, a close cooperation between clinicians and radiologists is needed (18, 19). MicroRNAs (miRNAs) are powerful regulators of gene transcription. Tubular epithelial cells robustly upregulate microRNA 21 (mir21) after renal ischemia (20). Chronic allograft nephropathy is the most common cause of kidney allograft loss and even with the implementation of recent immunosuppressant, the picture has not altered. Serum creatinine and glomerular filtration rate (GFR) have limited roles in estimating the histopathologic changes. Recent progress in the area of microRNA has hold a great promise to identify the renal fibrosis (21, 22). In addition, miR-142-5p is a promising biomarker for long-term renal allograft monitoring (22).

The HLA antibody tests are subdivided into cell-based and solid-phase tests. Cell-based tests include complement-dependent lymphocytotoxicity (CDC) and flow cytometric cross-match. Solid-phase tests include enzyme-linked immunosorbent assays (ELISAs) and multi-analyte bead tests either by flow cytometry or Luminex technology (23). Circulating donor-specific antibodies (DSA) against HLA class I or II have deleterious effect on the graft, and. Anti-class II DSAs promotes chronic rejection (24). Measuring the C1q-binding capacity of anti-HLA DSA

with the use of single-antigen flow bead assay determines its complement fixing capacity and its graft damaging capacity. C1q testing could identify at-risk patients who are C4d negative during the immunohistologic study of renal allograft (25). A dose-response curve does exist between DSA levels and intra-graft C4d deposition (26).

Luminex cross-matching is a powerful measurement for detection of DSA against HLA class I. With mean fluorescence intensity (MFI) ≥ 900 , Luminex cross-matching gives the best prediction of antibody-mediated rejections (AMR) (sensitivity of 75% and specificity of 90%) (27, 28). Pretransplant DSA could tailor the intensity of immunosuppression in sensitized patients (29). Increase of DSA one week after transplantation is a risk factors for rejection in sensitized patients and MFI > 3000 is in favor of future allograft C4d deposition (30). High risk patients benefit from antibody-depleting therapies and DSA monitoring, even beyond the first year of transplantation (24).

3.3. Special Posttransplant Events

Posttransplantation malignancies are important complication and are influenced by the degree of immunosuppression, viral infections, and recipient age. Squamous cell carcinoma of the skin is the most common malignancy and affected patients have a five-fold increased risk of developing another solid tumor (31). In European population, posttransplant lymphoproliferative disorders (PTLD) are the second most common malignancies and the same features were founded in a report from Iran (32-34). Geographic distribution of human herpes virus type-8 and Epstein-Bar virus (EBV) infections are important risk factors for Kaposi sarcoma and PTLD development, respectively (33, 34).

Genetic factors affect the susceptibility of insulin secretion capacity in pancreatic islets cells and its inhibition by calcineurin inhibitors (CNI) and hence, development of new-onset diabetes after transplantation (NODAT) (35, 36). Metformin has protective roles on the development of NODAT (35, 36). Posttransplant thrombotic microangiopathy is an important and confusing condition, which manifests with anemia thrombocytopenia and renal dysfunction, and transplant physician should be familiar with its unusual features (37-39). Hyperparathyroidism and its adverse effects could be continued after renal transplantation (40).

3.4. Specific Post Transplant Infections

BK virus (BKV) nephropathy continues to be a major concern. It develops after viruria and viremia phases. Urinary decoy cell surveillance using a cutoff of > 10 cells/hpf is a useful screening strategy (41). Tacrolimus increases the risk of BK infection; BKV-specific T-cell immunity and natural-killer cell receptor genotype are predictors of immune response to BKV and therapeutic outcome (42). Cytomegalovirus (CMV) is the most important viral

infection after renal transplantation and presents with different pictures (43-45). Inadequate treatment of CMV leads to emergence of resistance strains (46, 47). Majority of organ donors and recipients in developing countries are seropositive for anti-CMV IgG antibody (D+/R+), but even in this group, there are 49% chance of developing viremia (46, 47). Late-onset CMV affects the allograft two years after transplantation and predisposes the allograft to intense interstitial fibrosis (46, 47). Parvovirus B19 has special feature in renal transplant recipients and could be present as a combination of allograft dysfunction with pancytopenia (48, 49). Bacterial infection of the renal allograft could happen during the early periods of transplantation (50). Aspergillosis is a fatal infection and easily expands, particularly during the maximum immunosuppression (51). Mycobacterial infection is very common in developing countries where there are active transplantation program. Transplantation could exacerbate the course of leprosy and should be considered when there are suspicious skin lesions, particularly in endemic areas (52, 53).

4. Conclusions

Viral hemorrhagic fever infections (VHF) do exist in Middle East region and Iran. Arboviral hemorrhagic fever should be considered in the differential diagnosis of aseptic meningitis and encephalitis. Prevention of arboviral disease depends on community and household efforts to reduce mosquito densities (54-56). In addition, hemorrhagic fever with renal syndromes (HFRS) is responsible for renal dysfunction in the endemic region and can affect the native or allograft kidneys (56). Bacterial infection-associated glomerulonephritis needs special consideration in Middle East region. Brucellosis and periodontal diseases could be the underlying cause of active glomerulonephritis and renal allograft involvement (57, 58). Renal involvement of familial Mediterranean fever (FMF) and Behçet's disease needs specific consideration in the Middle East region, particularly in Turkish-Azeri ancestries. Patients with FMF who lost their allograft should continue their anti-inflammatory therapy even after renal transplantation. FMF-induced fever attacks and serum creatinine elevation could happen after transplantation and misdiagnosed as a systemic microbial infection (59-61). Gelsolin amyloidosis is a rare cause of familial amyloidosis and renal failure. Facial nerve paresis and skin involvement in the form of cutis laxa are its specific features and are reported from Middle East region. In gelsolin amyloidosis, renal outcome is excellent after transplantation (62, 63). Traditional herbal medicine are prevalent in developing country and they are often considered natural and safe while some of them are potentially nephrotoxic and impose risk on both native and allograft kidneys (64). We need to combine the global scientific vision with our local vigilance to deliver the utmost help to our renal transplant recipients.

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