

Acute rejection after pediatric kidney transplantation at Queen Rania Abdullah Hospital for children –Jordan

Mahdi Qasem Frehat, MD. Reham Issa Mardini, MD*. Ghazi moh'd Al-salaita, MD*. Jwahr Thiab Al-bderat, MD*. Aghadir Mohammad Alhadidi, MD*

ABSTRACT

Objective: Acute kidney rejection (AKR) is considered one of the most important medical post-transplant complications. It is associated with significant percentage of graft outcome of our patients with AKR. Our aim of this study is to clarify our center incidence of acute rejection and to discuss our experience in treatment of acute rejection.

Methods: This is a retrospective chart review study conducted in Queen Rania Abdallah Hospital for children which is a referral center in Jordan for pediatric kidney transplant, for all children who underwent kidney transplant and followed by the nephrology department over a period extended between 2004 and 2018. The age of patients ranged from 4-14 years. We studied the files of all the transplanted patients and who developed AKR. The following data were recorded: age of patients at the time of kidney transplant, sex, the primary disease, relation to the donor, time when acute rejection developed after kidney transplant, and being preemptive transplant or not.

Signs and symptoms at the presentation, creatinine level post rejection, histopathologic features on kidney biopsy, immunosuppressant drugs post kidney transplant and the treatment modalities of acute rejection all were reported for each patient.

The outcome of the treatment in the form of graft loss and the mortality were reported in the study.

Results: The total number of patients who received kidney transplant during the last 15 years from 2004-2018 was 127. With male to female ratio was 1.2:1. 24 patients (18.9%) developed acute rejection (AR). Acute cellular rejection (ACR) accounts for 79.2% (19 patients) while acute antibody mediated rejection (a AMR) 20.8% (5 patients). Mean age of kidney transplant patients was 10.2 ± 3.6 years. The most common primary causes that end up with acute cellular rejection were neurogenic bladder (33.3%), focal segmental glomerulosclerosis (23.8%). The acute mediated antibody rejection was seen in 3 patients with focal segmental glomerulosclerosis and in 2 patients with reflux nephropathy. 33% of patients with AR lost their grafts and mortality rate was 12.5%.

Conclusion: Acute kidney rejection is a serious complication post kidney transplant. Early diagnosis and compliance to treatment have a great impact on the outcome of AR.

Key words: Acute cellular rejection (ACR), Acute rejection (AR), Antibody mediated rejection (AMR), Kidney transplant.

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Introduction

Acute renal allograft rejection is deterioration in the kidney function associated with pathological changes in the kidney biopsy usually in the first year post-transplant but more often occurs in the first six months post-transplant where after that it mostly associated with noncompliance of immunosuppressive drugs.

From Departments of:

* Pediatric, Nephrology division, Queen Rania Hospital for children, King Hussein medical center (KHMC) Amman-Jordan

** Pediatric, Queen Rania Hospital for children, King Hussein medical center (KHMC) Amman-Jordan

Correspondence should be address to Dr Mahdi Frehat. Email mahdifarah70@yahoo.com.

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In general it is divided into two major types according to the histopathology: acute antibody-mediated rejection and acute cellular rejection with some cases have mixed type.⁽¹⁾

There is a dramatic fall in the incidence of acute rejection in the recent years due to introduction of potent immunosuppressive drugs but still there is challenge to decrease the associated side effects of these drugs.

The percentage of kidney transplant recipients experiencing an acute rejection during the first year post-transplant has declined steadily since 1996 and has stabilized in recent years.⁽²⁾ In 2013, 7.3% of living donor transplant recipients and 7.5% of deceased donor transplant recipients experienced at least one acute rejection during the first year post-transplant.⁽²⁾

Acute renal allograft rejection is a major cause of allograft dysfunction and it could lead to permanent loss of the allograft even with maximal anti rejection treatment especially those that occur in the first two months post kidney transplant. A large study conducted in the United States of America reported that 7% of all acute rejection episodes (ARE) result in graft loss and/or patient death.⁽³⁾ Even for those who respond to treatment there is an increased chance to develop chronic allograft nephropathy which is associated with high risk of graft loss and mortality after the first year.⁽⁴⁻⁶⁾

With the use of modern immunosuppressive drugs the acute renal allograft rejection is rarely associated with symptoms like fever, oliguria, graft pain or hypertension. So continuous follow up of kidney function test mainly the creatinine is important to detect acute rejection.⁽⁷⁾

The kidney biopsy still forms the gold standard method to diagnose the acute rejection and to subdivide it into the two major types. Acute cellular rejection (ACR) and acute antibody-mediated rejection (aAMR). Both of the two types differ in the treatment and some cases have both component.

Acute antibody-mediated rejection (aAMR) after renal transplantation (RTx) is defined as acute deterioration of kidney function combined with development of donor-specific antibodies (DSA) or reactive antibodies (e.g. ABO isoglutinins, anti-endothelial antibodies) and characteristic histological signs, such as capillaritis and glomerulitis and positive staining for C4d.⁽⁸⁻⁹⁾ Acute cellular rejection (ACR) is characterized by interstitial infiltration with mononuclear cells, tubulitis, and intimal arteritis.⁽¹⁰⁾

Over the last two decades there is introduction of new immunosuppressant drugs for post kidney transplant and new modality of treatment of acute renal rejection.

Up to our knowledge there is no study conducted in our country about the acute renal rejection so we reported our experience in Queen Rania hospital for children which is a referral center in the country for pediatric kidney transplant, in the types of rejection, presentation and mode of treatment over 15 years.

Method

A retrospective chart review study involved all children who underwent kidney transplant over the last 15 years during the period (2004-2018) in Queen Rania hospital for children/ King Hussein Medical Center which is a tertiary hospital for pediatric nephrology kidney transplantation. The age of children ranged between (4 -14 years) The following demographic data were recorded for each patient: age of patients when kidney transplant were done, sex, the primary disease, donor, time when acute rejection developed after kidney transplant, preemptive transplant.

Signs and symptoms at the presentation, creatinine level pre and post rejection, and immunosuppressant drugs post kidney transplant and the treatment for acute rejection all were reported for each patient.

The outcome of the treatment in the form of graft loss and the mortality were reported in the study.

At our center the regular follow up protocol after kidney transplantation includes kidney function test, complete blood count, urine analysis, urine output, blood pressure, serum immunosuppressants level, CRP, ALT, AST, Anti CMV IgM, Anti EBV I gM, and transplant ultrasound. Protocol Kidney biopsy is not part of our follow up and the indication for kidney biopsy is for symptomatic patients with rising creatinine level.

Each patient with deteriorated kidney function test (increase in the creatinine level more than 20% of the baseline.) should have renal ultrasound to rule out obstruction and renal Doppler ultrasound to assess the blood supply of the graft by measurement of resistive index RI index, Measurement of the plasma calcineurin inhibitor concentration to exclude acute calcineurin inhibitor toxicity and CMV and BK viral load before kidney biopsy.

Diagnoses of acute kidney rejection types depend on pathological changes in the kidney biopsy. ACR shows the following pathological changes: interstitial infiltration with mononuclear cells and occasionally eosinophils, disruption of the tubular basement membranes by the infiltrating cells (ie, tubulitis) ⁽⁸⁾, and arteritis. (AMR) of renal allograft needs at least 3 of the following histologic features.⁽¹¹⁾

- Neutrophil/lymphocyte margination (capillaritis)
- Thrombosis/necrosis

- C4d+ in peritubular capillaries (PTC)
- Circulating anti-donor antibodies (DSA)
- T cell mediated rejection
- Acute tubular necrosis (ATN)

C4d-negative antibody-mediated rejection” is now widely recognized⁽¹²⁾

In our hospital we don't do DSA right now and we depend in diagnosis of acute antibody mediated rejection on positive finding of kidney biopsy

Pre-transplant complement-dependent cytotoxicity crossmatches were negative and ABO compatible in all patients

The study was approved by the ethical and research review board committee of the Jordanian Royal Medical Services.

We used the percentage and the standard deviation in analyzing the some result as age. All statistical analyzes were performed using SPSS version18 (SPSS Inc., Chicago, IL, USA) and $p < 0.05$ is considered to be the significant difference.

Result

The total number of patients who underwent kidney transplant during the last 15 years from 2004-2018 was 127. With male to female ratio was 1.2:1. 24 patients (18.9%) developed acute rejection (AR). Acute cellular rejection (ACR) accounts for 79.2% (19 patients) and acute antibody mediated rejection (a AMR) 20.8% (5 patients). 20.3% of recipient male patients developed AR and 17.2% of females developed acute rejection. Male to female ratio was more in the (a AMR) category as shown in (Table I).

Mean age of kidney transplant patients was 10.2 ± 3.6 years and the mean age for whom developed acute rejection was 11.7 ± 2.1 years. Mean age of acute cellular rejection was 11.9 ± 2.8 years and acute mediated antibody rejection was 11.4 ± 2.9 years. (Figure 1)

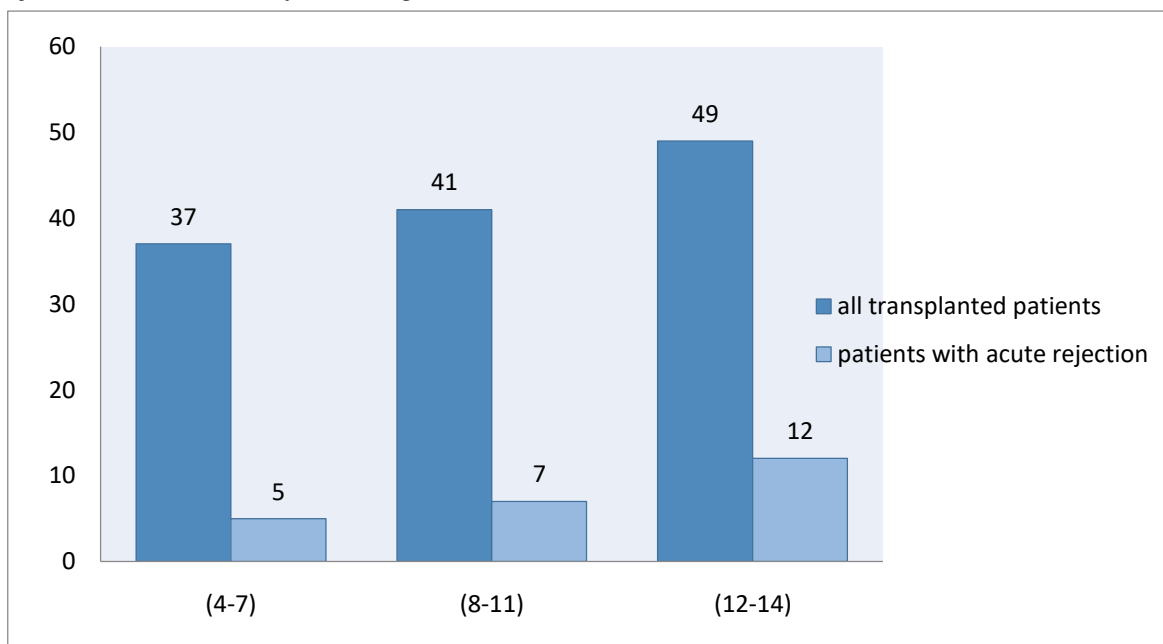


Fig1: The Number of Transplant Patients and who developed rejection According To Age Groups- years

96.1% of the kidney transplants were from living donor, 88.2% are from relative, and 3.9% from deceased donor. Mean age of the living donor was 38 years. 40%, 30%, 17% of deceased, not relative and related living donor transplants respectively end with AR.

Preemptive transplant accounts for 27.5% of our patients. 14.3% of these patients developed acute rejection and 20.7% of the non-preemptive transplanted patients developed acute rejection. P value 0.01. (Table I)

Dysplastic kidney disease, focal segmental glomerulosclerosis and reflux nephropathy account for more than 50% of primary causes in recipients. The most common primary causes that end up with acute cellular rejection were neurogenic bladder (33.3%), focal segmental glomerulosclerosis (23.8%), Rapid progressive GN (12.5%), Dysplastic kidney disease (11.1%), reflux nephropathy (10.5%) all of these account for 73.7% of the primary

causes in the acute cellular rejection. The acute mediated antibody rejection was seen in three patients with focal segmental glomerulosclerosis and in two patients with reflux nephropathy. (Table II)

Hypertension, fever and oliguria were the most common presentation in acute rejection. But still there is significant percentage of patient's is asymptomatic 41.7 %.(Table III)

Table I: Demographic characteristic of the all transplant patients and who developed acute cellular rejection and acute antibody-mediated rejection.

Variables	All Patients with kidney transplant (127 patients)	Patients with acute renal rejection	
		Acute cellular rejection (19 patients)	Acute antibody rejection (5 patients)
Age of recipients (mean±SD)	10.2±3.6 years	11.9±2.8	11.4±2.9
Male / female	69/58 (1.2:1)	11/8(1.4:1)	3/2(1.5:1)
Donor:			
Cadaveric	5	2(40%)	0
Living:			
Related	112	15(13.4%)	4(3.6%)
Not related	10	2(20%)	1(10%)
Preemptive transplant	35/127(27.5%)	4/19(21.1%)	1/5(20%)

Table II: Primary causes of end stage renal disease in transplanted patients, who developed acute cellular rejection, and acute antibody mediated rejection.

Primary causes of ESRD	All transplant pts	Acute rejection	
		Acute cellular rejection	Acute Antibody mediated rejection
Dysplastic kidney disease	27(21.3%)	3(11.1%)	
Focal segmental glomerulosclerosis	21(16.5%)	5(23.8%)	3(14.3%)
Reflux nephropathy	19(15%)	2(10.5%)	2(10.5%)
nephronophthisis	10(7.9%)	1(10%)	
Rapidly progressive GN	8(6.3%)	1(12.5%)	
Neurogenic bladder	6(4.7%)	2(33.3%)	
Membranoproliferative GN	5(3.9%)		
Bartter syndrome	3(2.4%)		
Posterior urethral valve	2(1.6%)	1(50%)	
Epstein syndrome	2(1.6%)	1(50%)	
AD polycystic kidney disease	2(1.6%)	1(50%)	
AR polycystic kidney disease	2(1.6%)		
Cystinosis	2(1.6%)		
Diffuse mesangial sclerosis	2(1.6%)		
Hemolytic uremic syndrome	1(0.8%)		
Pre-renal cause(acute pancreatitis)	1(0.8%)		
Otorenal syndrome	1(0.8%)	1(100%)	
unknown	13(10.2%)	1(7.7%)	

Table III: Symptoms and signs of acute rejection in the 24 patients

Symptoms and signs of presentation	Acute cellular rejection (19 patients)	Acute antibody rejection (5 patients)
fever	6 patients	2 patients
oliguria,	5 patients	1 patients
graft pain and tenderness	4 patients	0
Hypertension	12 patients	2
Asymptomatic with accidental rising of serum creatinine	9 patients	1
Pyuria	9 patients	1
proteinuria	7 patients	2
hematuria	5 patients	3
elevated resistance indices (RIs)	9	2

Most of the rejection occurs in the first 3 months post-transplant 55.5% and there is no difference between the acute cellular rejection and the antibody mediated rejection in the time to develop (Figure 2). Late rejection presented most commonly among the teenager with mean age of 12.6 years.

The incidence of rejection increases over the study period in (Figure 3) from 2008 the average percentage of rejection was 16.9%/year

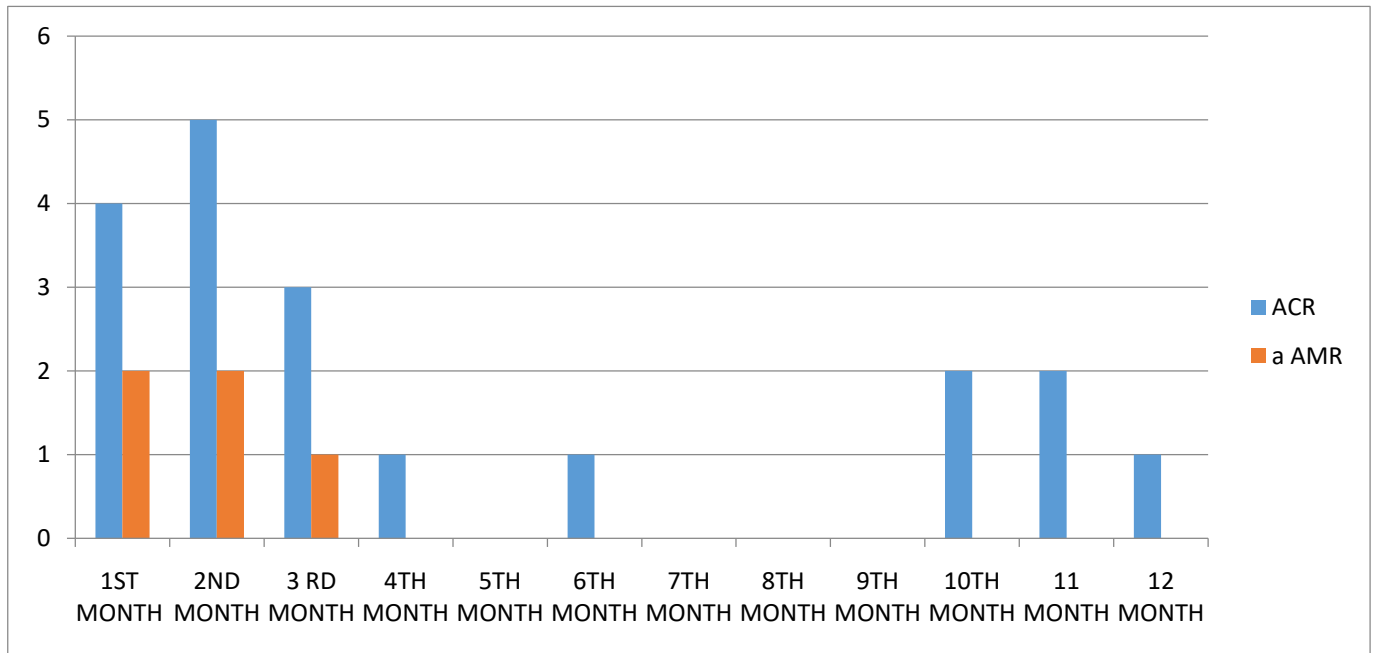


Fig 2: Time of presentation with acute rejection from kidney transplant. ACR: acute cellular rejection. a AMR acute antibody mediated rejection.

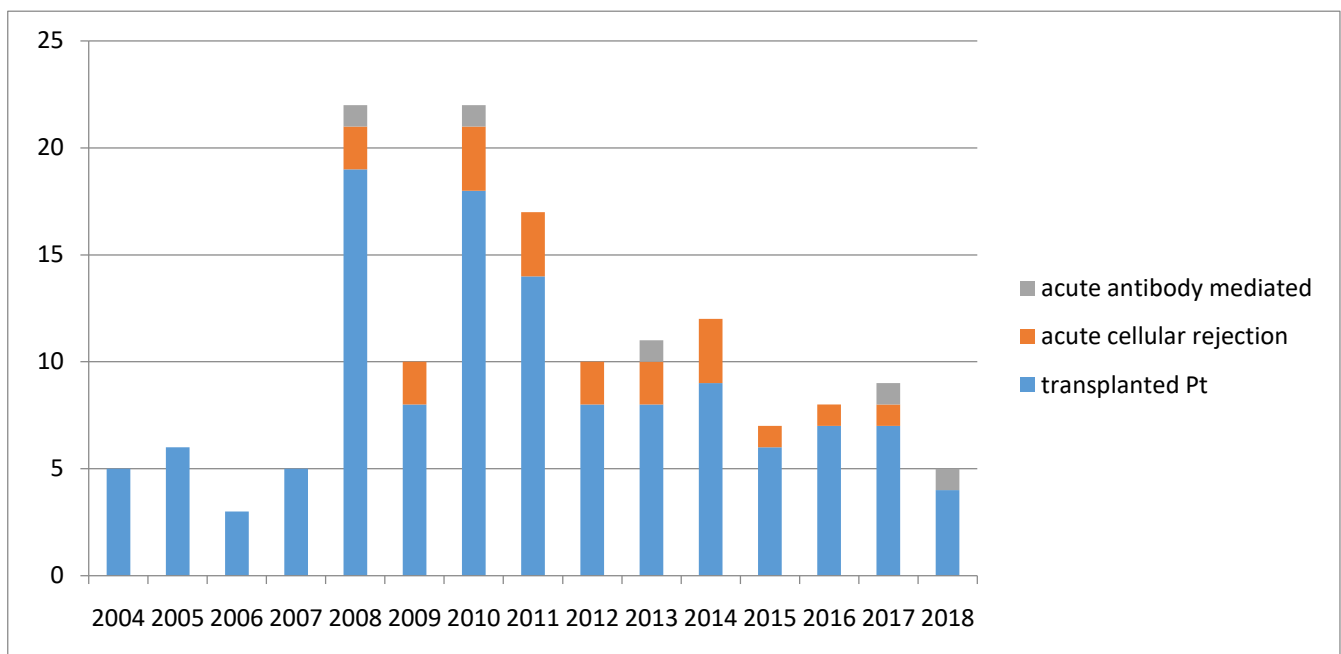


Fig 3: Distribution of transplanted patients, acute antibody mediated rejection patients and acute cellular rejection patients over years (2004-2018)

Of the total 19 patients who developed acute cellular rejection all of them received pulse methylprednisolone with dose 15mg/kg 3-5 doses. 10patients (52.6%) completely responded to the steroid therapy alone. three patients were steroid resistant with no improvement in the urine output or decrease in the serum creatinine level after five days of treatment so they received 3 doses of antithymocyte globulin (ATG)1.5mg/kg with complete

response. Six patients (31.6%) presented late to our clinic with high serum creatinine level (10-12 mg/dl) and didn't respond to steroid so maintained on hemodialysis, two patients died (10.5%) from pulmonary edema. Acute antibody mediated rejection which found in five patients started on steroid until the result of the kidney biopsy reveled the diagnosis of a AMR, four of our patients started on plasmapheresis 10 sessions and the one who didn't receive plasmapheresis presented late with creatinine 32 mg/dl and started on hemodialysis, unfortunately this patient died in the first two week after presentation due to pulmonary edema. Three of our patients received single dose of IVIG 2 g/kg after two days from the last session of plasmapheresis then given two doses of rituximab 375mg/m² two weeks apart as it was introduced to our protocol in the recent years. We used ATG after plasmapheresis in one patient who unfortunately lost his graft due to incomppliance on the immunosuppressant drugs. We achieved complete recover of the kidney function with normalized of creatinine and urine output within two weeks in three patients (60%).

Discussion

In the last 20 years the incidence of acute kidney rejection (AKR) has decreased from 70% before 1990 to 16% during the period 2007-2013. 45% of patients had at least one rejection in their life (40% in living donors and 49% in deceased donors) as reported by North American Pediatric Renal Trials and Collaborative Studies 2014.⁽¹³⁾ Two studies from Germany and Portugal reported the incidence to be higher than that seen in USA, 27.2% and 32% respectively.^(14,15) Another one from Brazil published in 2017, the incidence of AKR was 22%.⁽¹⁶⁾ Few studies published in our region showed that the incidence of AKR is different from one country to other, In Iraq 23%⁽¹⁷⁾, Egypt 47.3%⁽¹⁸⁾ and Iran 39.5%.⁽¹⁹⁾

The incidence of AKR is slightly higher in children than in adult (12.5% versus 11%)⁽²⁰⁾ This was attributed to an increased immunologic responsiveness in young children.^(20,21) In our study the incidence during the last 15 years was 18.9% which is considered to be a low incidence in comparison to other reported studies.

Incidence of acute antibody mediated rejection (a AMR) is 3%-10% of allograft transplants. And it accounts for 20%-30% of all the AKR.⁽²²⁾ A review of kidney biopsies that were done in one center taken from both adult and children showed that acute cellular rejection (ACR) was found in 14.1%, a AMR in 4%, and combination of the two rejections in 5.7%.⁽²³⁾ Other study was done in adult patients showed that the total population was divided into a AMR(39.2%), ACR (34.1%), and mixed acute rejection (26.7%).⁽²⁴⁾ We found the incidence of a AMR 3.9% of all the transplanted patients which accounts for 20.8% of all the rejection episodes and for the ACR 15% of all the transplanted patients and account for 79.8% of all rejection.

In most studies there is increase in the male percentage in the transplanted patients which is also found in our study and this could be explained by the fact that male patients comprise the majority of congenital anomalies and obstructive uropathy both of which account for the large percentage of the primary causes that end with end stage renal disease and needed transplant^(13,17) There is no difference between the male and female in developing the overall AKR but in acute a AMR there was more predominance of male than female, but because of the small number of patients who developed a AMR this could be not that significant.

The youngest age of the recipients in our hospital was 4 years old with body weight of 12 kg. In USA 20% of the recipients were less than six years.⁽¹³⁾ The mean age of our patients was 10.2 years which is similar to others.⁽¹⁵⁾

Most of the rejection occurred in the patients older than 12 years old during the duration of 2005-2013 in USA⁽¹³⁾ other study showed no effect of the age on the incidence or the outcome of the rejection.⁽²⁵⁾ The most age group that developed rejection was 11-13 years in our study. This could be explained by the high rate of non-adherence to the immunosuppressant drugs in the adolescent age group 31.8% and this was associated with high incidence of graft lost in 44% and late acute rejection in 23%⁽²⁶⁾ the transition from pediatric to adult medical services is an important time in the life of adolescent with renal transplant which occurs at age of 14 years old in our hospital as this period is associated with high risk of graft lost and development of renal rejection so the presence of a well-established transition program is critical in every institution.⁽²⁷⁾

More than half of the rejection episodes occurred in the first 3 months post-transplantation 55.5% and we didn't find difference between rejection type, age or gender with time of developing AKR and this finding was observed in other studies^(25,28) Early rejection within the first 60 days associated with higher incidence of developing chronic rejection.⁽²⁹⁾ Ten-year graft survival rates censored for causes of graft loss other than chronic rejection were 94%, 86%, and 45% for patients without AKR, with early AKR, and with late AKR, respectively.⁽³⁰⁾ Living none related kidney donation is prohibited by Jordanian law, 18 patients were followed in our clinic had received kidney transplant outside Jordan due to unavailability of a related donor. There is paucity of available deceased donors (DD) so we mainly depend on the relative LD mainly from parents. In the USA 49.7% of all transplants came from DD source, 39.5% came from a parent, with the remaining 10.8% coming from other

LD. Parents comprise 78.5% of LD. Unrelated donor account for 13.3%.⁽¹³⁾ In other country like Lithuania, approximately 90% of kidney transplantations are from deceased donors.⁽³¹⁾ 10 and twenty years graft survival is higher in related LD transplant compared with DD transplant.^(32,33) Complications rate was 9.67% for LD kidney transplant and 18.33% for DD kidney transplant.⁽³⁴⁾ We find that there is decreased risk of acute rejection in recipients of related donor transplant. This finding is shown by the NAPRTCS report 2014.⁽¹³⁾

The incidence of preemptive transplants range from 6-27% ^(13,15,19) some studies found that there is decrease incidence of AKR in this group of patients and improved the graft survival rate ^(35,36) others authors report that there is no statistical difference in the time to first acute rejection episode nor in the number of acute rejection episodes during the 1st year after renal transplantation between pre-emptive transplantation and pre transplantation dialysis patients.⁽³⁷⁾ Our result shows no statistically difference between both groups in the incidence of AKR.

The most common primary diagnoses in patients who underwent kidney transplant are aplastic/hypoplastic/dysplastic kidneys (in 15.8% of the children) and obstructive uropathy (in 15.3%). Focal segmental glomerulosclerosis (FSGS) is the third most common (11.7%) and continues to be the most prevalent acquired renal disease NAPRTCS 2014.⁽¹³⁾ 38% of patients with focal segmental glomerulonephritis developed acute rejection in our study this observation could be confirmed by a larger study as shown in (Table II)

CMV infection considered as a risk factor for graft lost.⁽³⁸⁾ There is an interacting relationship between the CMV infection and rejection: virus infection causes triggering the rejection of the allograft especially if the donor is CMV positive and the allograft rejection activating a latent virus.^(14,39,40) In our community; almost all are CMV IgG positive but IgM negative and so prophylactic gancyclovir is given for high-risk patients i.e CMV negative recipients and also for patients who received Antithymocyte globulin. This could explain the finding that we didn't had patients with CMV infection that lead to acute rejection but (four patients) of them developed CMV infection after had acute rejection.

Resistive index (RI) has been considered as the best ultrasonographic parameter in patients with allograft dysfunction ⁽⁴¹⁾ it is used as a marker of microcirculation injury and a sequence of interstitial edema in all graft dysfunction. A RI value > 0.7 was considered as abnormal.⁽⁴²⁾

The standard immunological work-up of our local transplant center consisted of a screening for HLA-class I HLA-A, HLA-B, HLA-C, HLA-BW. And the cytotoxic antibodies should be negative.

We depend on the diagnosis of rejection and determine which type on the clinical presentation and histopathology. The presence of nephro-pathologist is critical in each hospital where kidney transplants are done. (Image1&2).

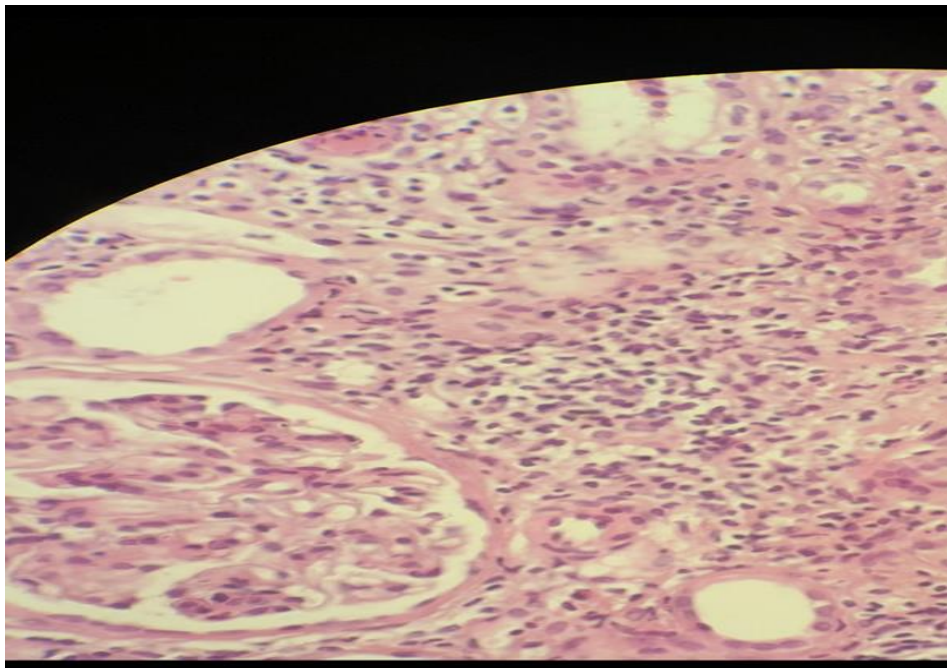


Image1: The interstitium shows dense lymphocytic cells infiltrate with focal lymphoid aggerates patchy foci of neutrophic and eosinophilic infiltrate are also seen The tubules show moderate cellular rejection with WBC cast and minimal loss.

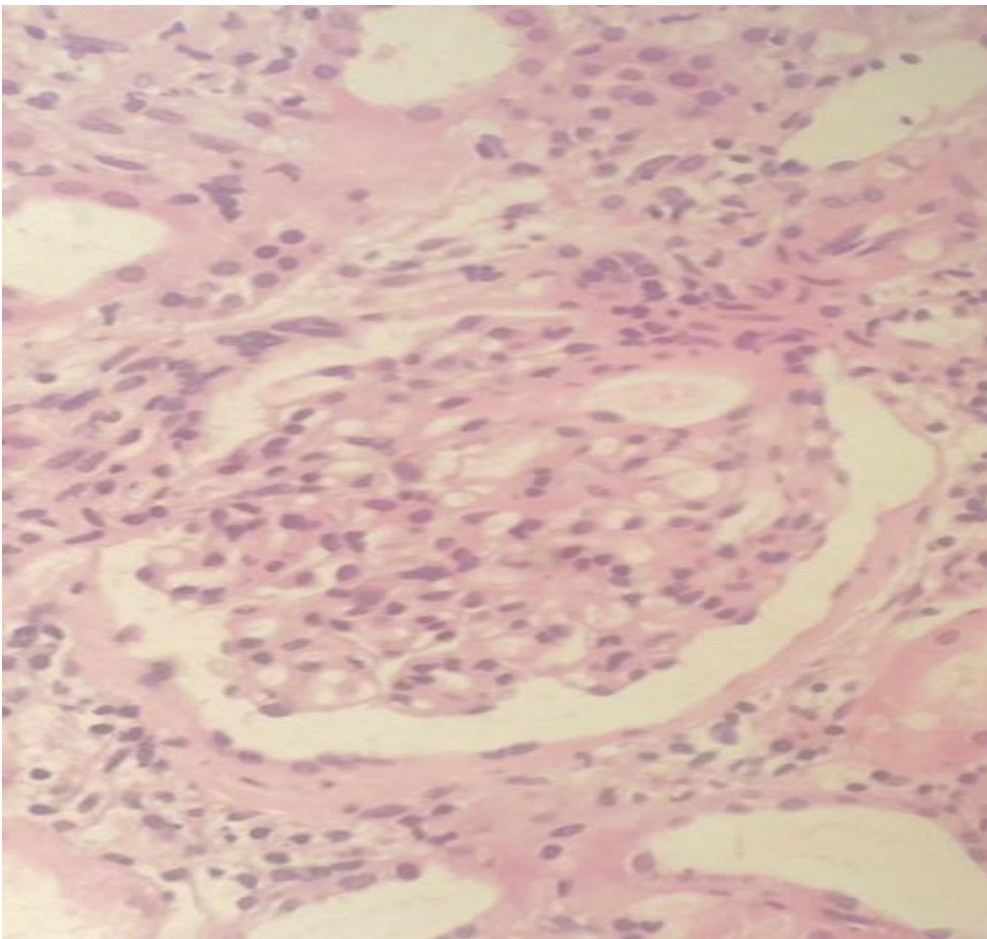


Image 2: The glomeruli show increase in mesangial matrix and cellularity with mild thickening of the glomerular capillary wall. Segmental glomerulitis is seen. Peritubular capillaritis. ptc3C4d immunostain is inconclusive. Features suggestive of antibody mediated rejection.

The incidence of rejection increases over the study period in (Figure 4) from 2008 this could be explained by increase the awareness of this diagnosis.

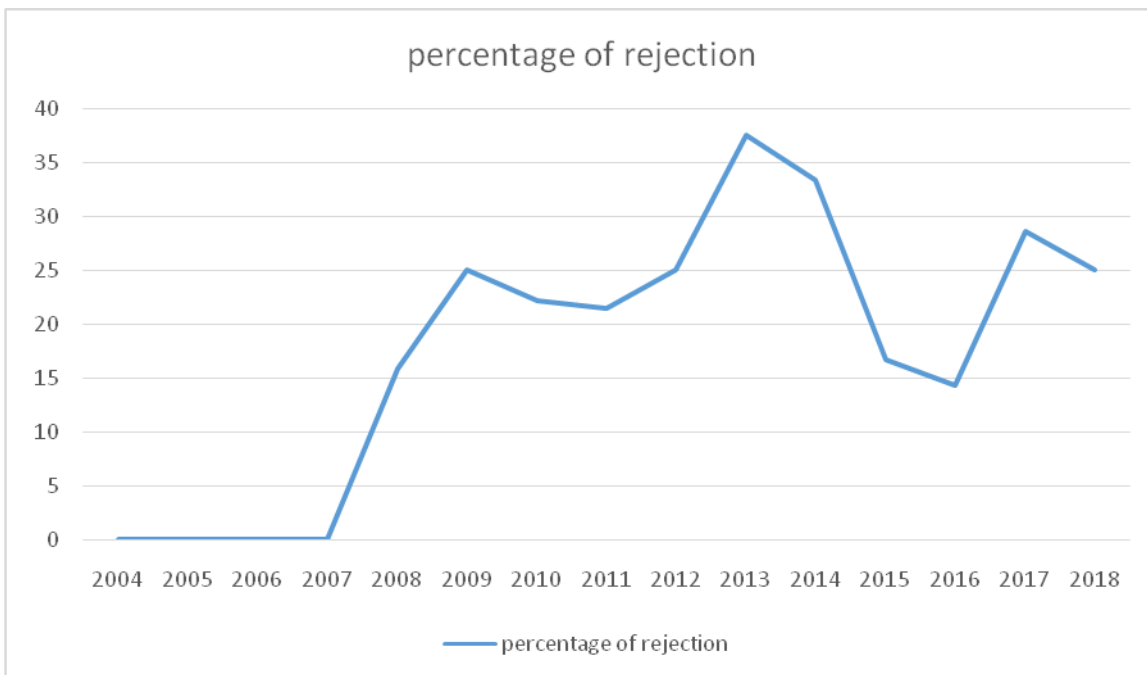


Fig 4: distribution of the percentage of acute rejection over years (2004-2018).

Our protocol of post-transplant immunosuppressant therapy starts with induction therapy including methylprednisolone giving during the perioperative period then the maintenance therapy on triple therapy

including calcineurin inhibitors mainly tacrolimus 0.2-0.3mg/kg/ day divided into two doses, antimetabolic agent such as mycophenolate mofetil 600mg/m2/dose twice daily and corticosteroid mainly prednisolone 2mg/kg/day then with gradual taper of the dose until reach 0.15mg/kg/day.

The first line of treatment for acute cellular rejection is methylprednisolone with full recovery obtained in the first 5 days of starting treatment was 52.6% other authors report 60-70%⁽⁴³⁾ in the patients who is steroid resistant anti T-cell antibody therapy should be started. There are two type of it: polyclonal antibodies, we use antithymocyte globin (ATG) in our hospital and in USA most commonly antibody use is Thymoglobulin. The other type is monoclonal antibodies (OKT3) but no superior benefit of the later. Less commonly used non antibody rescue therapies are tacrolimus and mycophenolate mofetil,

Antibody mediated rejection is more difficult to treat than acute cellular rejection. But with use of combined therapy of steroid pulses, IVIG, plasmapheresis and rituximab is potentially effective in the treatment of aAMR in children.⁽⁴⁴⁾ Steroid is started in all patients with acute rejection until the biopsy result determine the type of rejection and this will treat the cellular component of the rejection especially in the mixed cases. Plasmapheresis lead to removal of circulating antibody which improve the AMR.⁽⁴⁵⁻⁴⁸⁾ but there is no agreement on the number of sessions needed^(49,50) Antibody binding with IVIG.⁽⁵¹⁻⁵⁴⁾ An effective basic immunosuppression with TAC and MMF (at least most transplant units use TAC as the primary calcineurin inhibitor in re-transplantations and/or patients with aAMR)^(45-47,49,55,56) Other modality of treatment B-cell depletion with rituximab^(54,57) B cell elimination is rapid, usually within one to three days and the effect lasts usually one to two years but the dose and numbers of infusions are variable and center dependent. Common side effects are infusion reaction and hypotension.⁽⁵⁸⁾ Others use of antilymphocyte antibodies (ATG or OKT3)

Rejection rate and mortality correlate with the patients' incompliance on the immunosuppressant drugs, which was more relevant in the adolescents and this was proved by the sub-therapeutic immunosuppressant trough levels.⁽⁵⁹⁾ This highlight the importance of having a well transitional program when the patient transferred from the pediatric nephrology clinic to adult nephrology clinic at age of 14 years in our hospital.⁽²⁷⁾ In our study the full recover from acute allograft rejection was 66.6% with no much difference between the acute cellular rejection (68.4%) and the acute mediated antibody rejection (60%). The main causes to treatment failure were presentation late to our clinic with very high creatinine level and incompliance on treatment mainly in the teenager patients. Mortality was 12.5%. The recent report published by NAPRTCS 2014⁽¹³⁾ revealed that the outcome in patients who received transplants from the living donor is better than deceased donor. The full recovery with the return of creatinine level to the base line is 52%, partial recovery 44%, and graft lost or patient death 5% in living donor graft recipients.⁽¹³⁾ A multicenter national report from Iran in 2011 showed that the rate of graft survival in patients with acute rejection is less than without acute rejection, it was 86% at the first year, 63% at the fifth year, and 53% at the 10th year after transplantation in patients who developed acute rejection and 92%, 85%, and 72% at the first, fifth, and 10th years, respectively, in whom didn't developed acute rejection.⁽¹⁹⁾

Conclusion

Early diagnosis and compliance to treatment have a great impact on the outcome of AR.

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