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An Overview on Common Viral Infections in Kidney Transplant Recipients

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Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

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ABSTRACT

The viral infections post transplantation are extremely important and guides us about the intensity of immunosuppressant and there monitoring guides us to fine tune the immunosuppression. Similarly the knowledge of the viral diseases post transplantation guides the transplant clinician to diagnose these diseases early and manage them before they become progressive.
Similarly blood transmitted diseases are much more common in resource poor countries. With lack of deceased donor program and paired kidney exchange in infancy we end up doing sensitised or ABO incompatible living donor transplants subjecting them to intense immunosuppressive regimens, which ultimately lead to the emergence of opportunistic viral infections such as CMV, BK and EBV.

Keywords: Viral infections; kidney transplant; donor transplants.

1. INTRODUCTION

The viral infections post transplantation are extremely important and guides us about the intensity of immunosuppressant and there monitoring guides us to fine tune the immunosuppression. Similarly the knowledge of the viral diseases post transplantation guides the transplant clinician to diagnose these diseases early and manage them before they become progressive.

Similarly blood transmitted diseases are much more common in most resource poor countries..

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With lack of deceased donor program and paired kidney exchange in infancy we end up doing sensitised or ABO incompatible living donor transplants subjecting them to intense immunosuppressive regimens, which ultimately lead to the emergence of opportunistic viral infections such as CMV,BK and EBV.

These viruses emerge because modern immunosuppression knocks down the different components of innate and adoptive immunity. This allows for chronic viral replication of some viruses like hepatitis B and C.

Similarly some viruses cause immuno-modulation and depresses immunity and predispose to other viral infections. In addition persistence of some viral infections can lead to malignancies.

Similarly immunocompromised host has dysfunctional immune surveillance system that cannot eradicate the oncogenic viruses. We will discuss viral diseases from different guidelines, consensus recommendations and relevant studies in the subject.

2. CYTOMEGALOVIRUS (CMV)

CMV Post Transplantation carries a significant morbidity and mortality and with reduced graft survival.CMV belongs to the 5th herpes group of viruses (HHV 5) with 4 genotypes. It primarily affects the immunocompromised host.

Seroprevalence is 60 percent. It can affect approximately 30 to 60 percent of the postransplant patients without prophylaxis or pre-emptive monitoring. Asymptomatic CMV in the first 3 months is associated with increased mortality. Majority are newly infected or there is activation of the latent virus.

2.1 Definitions and Clinical Manifestations

It is defined in 3 major ways:

CMV Infection is characterised by CMV in blood;
CMV Syndrome is manifested by CMV viremia and fever, malaise, leukopenia or thrombocytopenia and
CMV Disease- CMV syndrome and organ involvement is called CMV disease.

2.2 Indirect Effects of CMV

CMV can have variety of manifestations as part of their secondary affects. It is an immunomodulatory virus. On one hand it can predispose to other opportunistic infections especially fungal infections, on the other hand it can predispose to acute and chronic allograft injury as it can trigger an alloimmune response through its up-regulation of cytokines, adhesion molecules, and increased expression of major histocompatibility complex molecule[1].

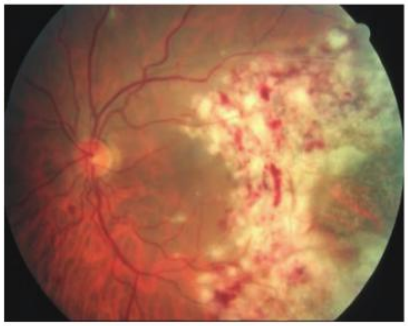

Fig. 1. CMV retinitis

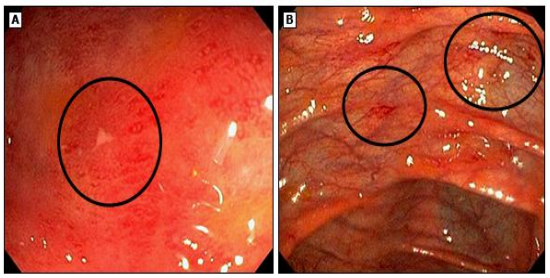

Fig. 2. CMV retinitis in transplant patients

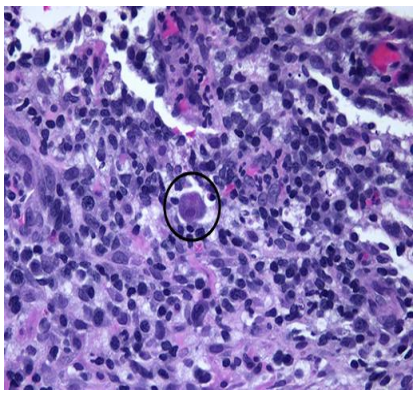

Fig. 3. CMV colitis in transplant pt

2.3 Transmission

It can be transmitted through blood or sex.

2.3.1 Time line

It usually affects from second to six months but now with prophylaxis there is incidence of late

onset CMV and usually after 1 month when the prophylaxis is finished.

2.4 Risk Factors

All the factors leading to increase intensity of immunosuppression, lymphocyte depleting agents, acute rejection episodes, neutropenia etc predispose to CMV as well as the donor and recipient risk status pre-transplantation.

2.4.1 Risk stratification for CMV

D+ R- high risk
D+R+ intermediate risk
D-R- low risk

The length of the prophylaxis and the decision between pre emptive monitoring and not give prophylaxis depends upon the risk status of CMV.

2.4.2 Diagnosis

PCR remains the main diagnostic tool for diagnosis of CMV infection. For CMV disease need tissue diagnosis either BAL or biopsy. The biopsy may show typical intra-nuclear inclusions of CMV along with immunohistochemistry for CMV antigen CMV viremia has to be also interpreted in light of risk status and symptoms of the patient.

With symptoms any level of viremia is considered significant for CMV diagnosis.

Similarly for high risk CMV status any level of viremia is considered significant. For intermediate or low risks in solid organ transplants a viral count more than 1000 is considered significant in asymptomatic patient. On the other hand viral copies more than 1700 are considered significant for asymptomatic HSCT transplants [2].

Tissue invasive CMV disease can have a negative PCR for CMV especially in the patients who are on mycophenolate moefitil.

CMV PP 65 antigen is less used because of lack of standardisation and the samples need to be processed urgently.

Viral cultures have also poor sensitivity and long turn over time.

2.4.3 Prevention

CMV prevention has 4 approaches, the first one is antiviral prophylaxis for postransplant patients depending upon their risk status, High risk for CMV it is recommended to give valgancyclovir for 6 months and some researchers recommend it for 9 months[3].

Intermediate risk CMV require 3 months of valgancyclovir, and the low risk will receive no prophylaxis for CMV but for herpes simplex. Patients who receive thymo as an induction agent, some researchers recommend 6 months of prophylaxis for intermediate risk CMV.

The other approach is pre-emptive CMV monitoring every week for 3 months post transplantation and, when viremia reaches a predefined level anti-virals are started. The rate of multiplication of CMV viremia is more significant than a single value. The anti-virals are continued till CMV is negative and PCR repeated in a weeks' time.

The advocates of prophylaxis suggests that valgancyclovir can cover other herpes viruses and is associated with less rejection episodes.

The advocates of pre-emptive monitoring suggest that there is increase incidence of late onset CMV with prophylaxis.

The third approach is a deferred therapy for monitoring of patients for CMV and treatment of symptomatic patients only.

Fourth approach is treatment based on detection of active CMV with signs and symptoms of CMV without monitoring.

MTOR inhibitors decrease the incidence of CMV has been demonstrated by some researchers.

Valcyclovir prophylaxis have equivalent results also. Patients who receive ATG as a part of treatment of T-cell mediated rejection should receive prophylaxis for CMV or pre-emptive monitoring [3].

In heart and lung high risk CMV TPL recipients, CMV specific IVIG in combination with viral prophylaxis can be used.

Leucopenic transplant recipients can be given letermovir which is a potent nanomolecular inhibitor of the UL56 component of the terminase complex as a prophylactic agent in place of valgancyclovir.

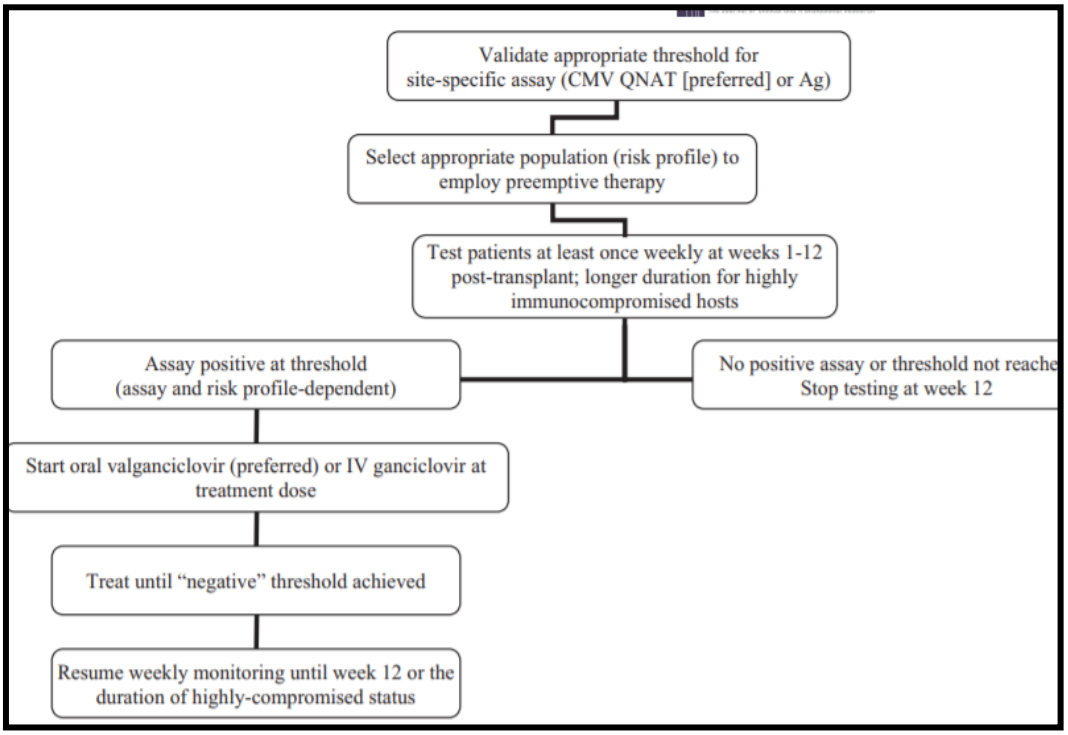

Fig. 4. AST CMV guidelines 2019 an algorithm for pre emptive CMV monitoring

2.4.4Treatment of CMV

Treatment options for CMV disease are mainly 2 drugs,IV ganciclovir or valgancyclovir. For tissue invasive CMV disease,IV ganciclovir is better. It should be administered for a minimum of two weeks or till the resolution of clinical symptoms, and CMV viremia is undetectable on two consecutive samples a week apart.

The new CMV guidelines do not recommend secondary prophylaxis.

Patients with CMV disease who began therapy initially with IV ganciclovir, after clinical and virological control can be shifted to valganciclovir.

High dose gancyclovir, first and then foscarnet with its nephrotoxic potential is used in cases of resistant CMV with UL97 mutations. With the other Ul54 mutation virtually nothing works, as it manifests cross resistance to cidofovir and other viral agents. Cell-mediated immune specific assays to CMV for identification of risk are available but further studies are needed before being utilised widely in clinical practice.

2.4.5 Resistant CMV

Resistant CMV is defined as no response to 2 weeks of antiviral treatment. The viral copies do not fall by 1 log [4].

In patients who have resistance to gancyclovir, mutations should be seen in UL97 component. Whereas mutations in UL54 component should be seen in patients who demonstrate panresistance to other viral agents. In patients who demonstrate letermovir resistance should be checked for mutation at UL56 and UL51/ UL89.

Immunosuppression reduction is vital not only for gancyclovir sensitive CMV but also for resistant CMV.

Maribavir, letermovir can be used in UL54 mutations. The other options are IVIg or CMV specific pentaglobin in combination with antiviral drugs.

Adoptive transfer of CMV-specific T cells can be used in resistant CMV if access to it is there.

2.5 Epstein-Barr Virus

Epstein-Barr virus has a seroprevalence of more than 90% in adults. Clinically patients with EBV viremia can present with an infectious mononucleosis like illness to organomegaly and organ specific disease such as gastrointestinal, lung and CNS involvement and postransplant lymphoproliferative disease.

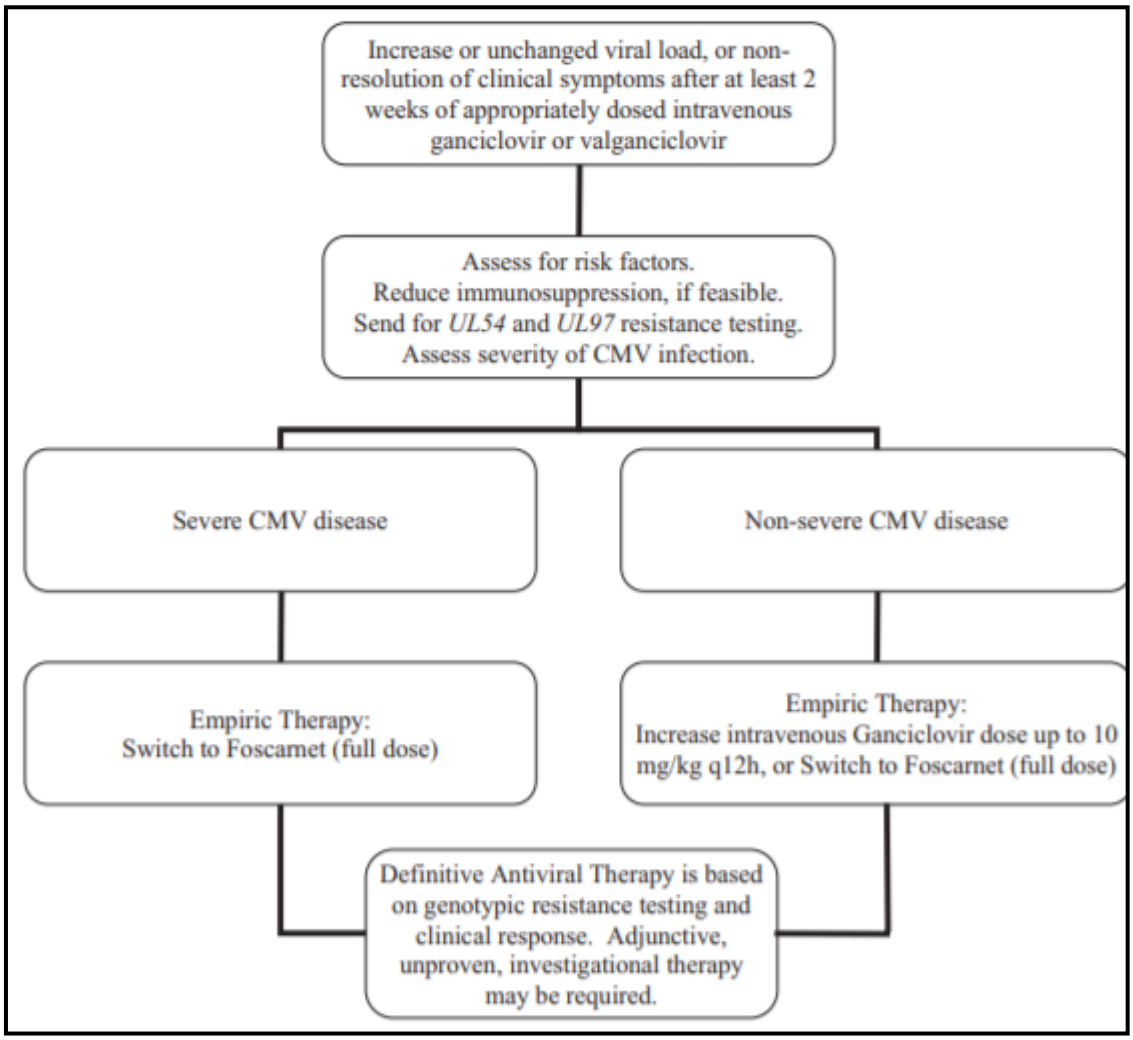

Fig. 5. AST CMV guidelines 2019 An approach to refractory or resistant CMV

The incidence of PTLD is lowest in renal transplantation as compared to other organ transplants. It has biphasic onset with cases occurring within 1 year of transplant or after 15 years of transplant.

EBV related disorders can be nodal or extra-nodal, localized, sometimes in the allograft, or widely spread. Sometimes the disease progress slowly or fulminantly.

2.5.1 Pathogenesis of EBV related PTLD

EBV infection has unique characteristics so pathogenesis is complex.

The virus first transforms B lymphocytes and immortalize them, and cause their proliferation. There are genetic and epigenetic mutations associated with this process.

Secondly, EBV blocks apoptotic cell death. EBV related PTLD occurs because complex mechanisms of gene expressions within the virus and host genetic changes are occurring within the cell [5]. The Immunomodulation caused by EBV lead to the tolerigenic environment between viral and cell RNA.

2.5.2 Risk factors for EBV related PTLD

The risk factors for PTLD are the same as other opportunistic viruses.

This includes EBV risk status D+R-, intensity of immunosuppression including lymphocyte depleting agents and co stimulatory blockade.

Similarly children are at high risk of PTLD, and some researchers recommend pre emptive EBV monitoring postransplant and using reduction of

immunosuppression or pre emptive rituximab for rising EBV DNA viremia [6].

Graft usually tends to get involved early in transplant. CNS PTLD and GI PTLD occurs later. No consensus exists regarding pre emptive EBV monitoring in adult population, what are the EBV viremia thresholds? When one starts responding to rising viremia by reduction of immunosuppression?.

2.6 Diagnosis

2.6.1 Viral load

Detection of EBV viremia is the key in diagnosis of PTLD in a clinical context.

The assay has not been standardised. T-cell ELISPOT assay added to viremia can improve the specificity for diagnosing PTLD especially in the early postransplant period.

2.6.2 Radiology

Second best diagnostic tool is radiology from conventional CT, MRI to PETCT.

CT can define the oropharyngeal involvement and can pick up subtle changes that will require a biopsy to rule out PTLD. Lung involvement can be visible on chest xray but usually require an HRCT before deciding regarding biopsy.

In addition HRCT can also give information regarding mediastinal lymphnodes and pulmonary nodules that may not be visible on the simple chest radiograph. The intra-abdominal lesions which are suspicious can be further evaluated with CT. For GI pathology needs endoscopy.

PET scan has increased sensitivity and specificity for PTLD, and locating biopsy site, and also for diagnosing relapse.

2.7 Histopathology

The histopathology is the gold standard. Although excisional biopsy is preferred, core biopsy can be performed where excision biopsy is impractical like allograft. After biopsy PTLD is classified as:

2.7.1 Non-destructive PTLDs

1. Plasmacytic hyperplasia
2. Infectious mononucleosis
3. Florid follicular hyperplasia
4. Polymorphic PTLD
5. Monomorphic PTLD

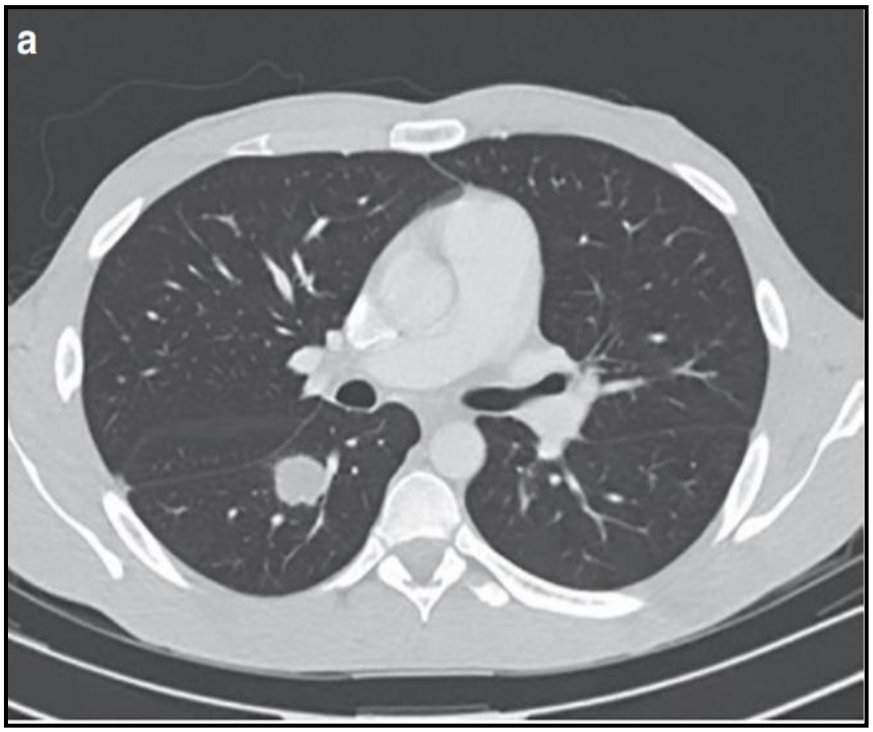

Fig. 6. PTLD in lung

2.7.2 B-cell neoplasms

1. large B-cell lymphoma
2. Burkitt lymphoma
3. Plasma cell myeloma
4. Plasmacytoma

2.7.3 T-cell neoplasms

1. Peripheral T-cell lymphoma,
2. Hepatosplenic T-cell lymphoma
3. Hodgkin lymphoma PTLD

2.7.4 Prevention

The role of prophylaxis in prevention of PTLD remains controversial even in high risk recipients EBV D+R**-.**

2.8 Treatment

2.8.1 Pre emptive management

This includes serial monitoring of EBV DNA, especially in high risk recipients. D+R- and acting accordingly with rise of EBV DNA, with reduction of immunosuppression. This approach reduces the onset of clinical PTLD. The problem is that assays of EBV DNA are not standardised and what is the threshold of viral load of EBV viremia where we start reducing immunosuppression?

Adoptive immunotherapy with cytoxic EBV specific T cells grown in vitro or third party donor can be used for prevention of PTLD in those patients who are not responding to reduction in immunosuppression [7].

Pre emptive rituximab can be combined with reduction in immunosuppression in patients when the EBV viremia crosses the defined threshold.

Regarding clinical PTLD also reduction in immunosuppression is the first step in management of EBV PTLD. Next step is rituximab along with reduction in immunosuppression. Surgical resection and radiation therapy can be used for localised disease. Cytotoxic therapy consisting mainly of vincristine, cyclophosphamide and prednisolone along with rituximab is used for advanced disease.

Adoptive immunotherapy can be used in refractory disease also. Immunomodulatory and anticytokine therapy can be used with IL6 blockers or PD1 inhibitors. The PD1 inhibitors can be associated with increased incidence of rejection.

2.8.2 Retransplantation in PTLD

There are case reports of successful re-transplant in patients with history of PTLD without recurrence. Would want remission of PTLD to be at least 2 years. Would not use induction with thymoglobulin, could consider simulect and Rapamune for IS after living donor kidney transplant in addition to low dose tacrolimus or Cyclosporin.

2.9 BK Polyomavirus

2.9.1 Introduction

BKV is a member of the Polyoma family and a double stranded DNA virus.

It can cause tubulointerstitial nephritis,stricture in the urethra,nephropathy (BKVAN), and an early graft loss.In haemopioetic stem cell transplantation it can cause haemorrhagic cystitis. Its seroprevalence in adults is between 40 -60 percent.

After inoculation of the BKV infection through respiratory or oral route, it remains latent in tubular epithelial cells of the kidney.

2.10 Risk Factors

Its risk factors remains the same as CMV,or PTLD in regarding intensity of immunosuppression, all factors related to it ie sensitised patients, acute rejection episodes, steroids, lymphocyte depleting agents, other risk factors include (D+/R-)Bk virus serology, deceased donor, older recipient, females, Anca vasculitis, being on haemodialysis, presence of ureteric stent, repeated antirejection therapies ,tacrolimus-MMF(mycophenolate) combination, or in case of re-transplantation when graft loss was due to BK nephropathy.

2.10.1 Diagnosis and screening

Incidence of BK viruria is between 20 -70 percent, wheras that of BK viremia is in the range of eight to fifteen percent.

The incidence of BK nephropathy is three to seven percent, and being higher in the first 3 to 6 months of transplantation.

Recommendations for BKV screening is by checking PCR for BK virus in the serum monthly

for first 9 months and then every 3 monthly till two years post transplant.

Then it can be checked annually upto 5 years postransplant.

BK viruria is not specific for BK nephropathy.

When the viruria is more than million copies then they start appearing in the plasma.

BK viremia with a viral load greater than 10,000 serves as a surrogate marker for BK nephropathy. When the Bk viral load is greater than 100,000, it is associated with extensive PyVAN pathology by SV40 stain and interstitial infiltrates.

BK is a progressive disease if immunosuppression is not cut down at appropriate time.

Half of the patients with high level viruria will progress to viremia in 2-6 weeks time and another half will progress to BK nephropathy in 2-6 weeks time.

Biopsy still remains the gold standard for diagnosis of BK nephropathy with viral cytopathic changes on light microscopy and using SV 40 stain by immunohistochemistry.

Because of the focal nature of the disease BK nephropathy can be missed on biopsy, especially in patients whom biopsy is done immediately after detection of DNAemia and biopsy core does not contain medullary tissue.

When the immunosuppression is reduced in BK nephropathy the virus is cleared from the kidney first and then viremia starts decreasing. In situ hybridisation and electron microscopy can be used to demonstrate viral particles. Urine decoy cells on fresh urine sample can also be used for its detection but its sensitivity and specificity is low.

2.11 Management

The corner stone of management of BK nephropathy is reduction of immunosuppression. There are 2 approaches to reduction in immunosuppression, one is withdrawl of mycophenolate completely, the other is reduction of CNI and MMF together by 50 percent. Both approaches work. The complete algorithm is described in Fig. 4 from AST guidelines 2019.

Regarding adjuvant antiviral therapy there is no robust data regarding their efficacy.

Cidofovir has been used at 1 week or 3 week intervals, dose adjusted to GFR, although there are studies which showed no benefit. Its nephrotoxicity and opthalmological side effects have to be kept in mind.

Similarly the efficacy of leflunomide and quinolones are restricted to case series and no randomised control studies have been done to show there efficacy.

In their paper they suggest efficacy of use of leflunomide in combination with ciprofloxacin along with reduction of immunosuppression. In that scenario it is difficult to tease out the effect of drugs whether it helped or reduction in immunosuppression helped. The next thing the study of leflunomide they are quoting number is restricted to 2.

IV IG is emerging as an important therapy in refractory BK who do not respond to immunosuppression reduction . A total dose of 2gm/kg should be administered in a single or divided doses. The problem is during IV IG administration how the PCR will differentiate between a live virus and dead virus. They are recommending to patients who are not responding to 8 weeks of reduction in immunosuppression. Again the study they are quoting is with leflunomide in combination.

The commercially available IV IG has more neutralising antiBK antibodies and should be used.

2.11.1 Re-transplantation in BK nephropathy

The patients who lose their graft due to BK nephropathy can be considered for re-transplantation after clearance of BK viremia. Graft nephrectomy is not required unless a live donor is available and there is urgency of transplantation. Re-transplantation should be considered with low immunological risk transplants so lesser immunosuppression and no induction is required, so there are less chances of BK reactivation in second transplants**.**

2.11.2 Hepatitis A virus

Most of the kidney transplant recipients with hepatitis C have HAV antibodies. It is

recommended that kidney transplant recipients with chronic liver disease or who possess risk factors for hepatitis A, but have negative antibodies should be given a vaccine. Hepatitis A can be transmitted through solid organ transplantation.

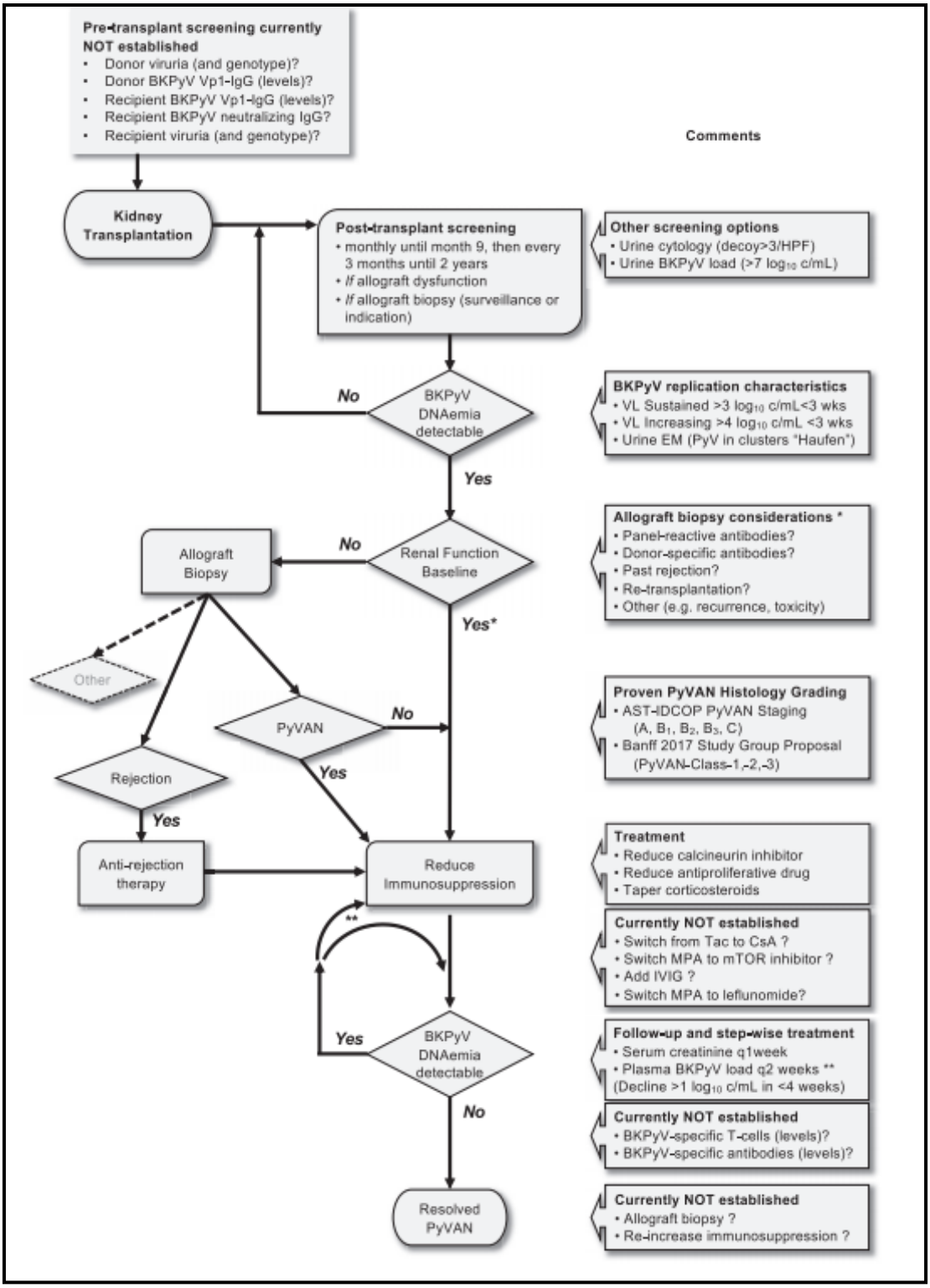

Fig. 7. Approach to screening and management of polyoma nephropathy .From AST guidelines 2019

2.11.3 Hepatitis B virus

Hepatitis B transmission is through blood,sex and organ transplantation.

Pretransplant evaluation of HBV infection is extremely important. Kidney transplant recipients with negative HBSag and negative core antibody should be vaccinated.

The HBSag positive recipients and core positive are further evaluated by HBV DNA,and if it is positive,concomitant infection with delta virus is excluded.The HBV DNA recipients should be started on entecavir/tenofovir before transplantation. Transplantation with high hepatitis B viral load increases the risk of fibrosing cholestatic hepatitis post-transplantation.

Core antibody positive donors are acceptable provided their HBV DNA is negative and the recipient has a protective immunity with antiHBs titres greater than 10.

2.11.4 Hepatitis C virus

The mode of transmission of hepatitis C is the same as hepatitis B.

In the era of direct antiviral agents hepatitis C positive kidney transplant recipients have an excellent survival rate, but the article mentions graft survival less than negative recipients.
The initial test for recipient and donor should be Anti HCV, if it is positive PCR for HCV should be done, after that genotyping should be performed.

Liver should be evaluated regarding the suitability for isolated kidney transplantation or simultaneous liver kidney transplantation should be considered.

DAA achieve ninety percent sustained viral response at twelve weeks.

HCV viremic deceased donors can donate to HCVnegative or HCV positive recipients, and post-transplant DAA'S are administered and they achieve more than 90 percent SVR.

Ultra short therapy with DAA'S in such scenario is emerging.

2.11.5 Hepatitis D virus

Mode of transmission is same as in Hepatitis B but requires the presence of hepatitis B to manifest its infection. Routine screening for HDV is not recommended unless there is a high level of suspicion. Data showed non recurrence of HDV viremia post HBV-HDV Co-infection once HBsAg clearance achieved post-transplantation. Bringing hepatitis B under control is sufficient to manage hepatitis D

2.11.6 Hepatitis E virus

Hepatitis E virus is a self limiting hepatitis, though fulminant hepatitis can occur in pregnant women and in patients with chronic hepatitis. The prevalence of HEV was found to be higher in developing countries.

The article quoted a study from france showing increased prevalence of acute hepatitis E in transplant population and significant proportion of that progressed to chronic hepatitis E.

Chronic hepatitis E can cause liver fibrosis and associated glomerular disease. Reduction in immunosuppression is the key in the treatment of chronic hepatitis E.

A retrospective study showed, that a 3 month course of ribavirin was used for [genotype 3] chronic HEV with 95% viral clearance and 78% SVR at 6 months. Pegylated IFN- alpha carries risk of allograft rejection due to its immunomodulatory effect.

2.11.7 Human immunodeficiency virus

With the emergence of modern HAART therapy kidney transplant recipients with or without HIV have a comparable graft or patient survival rate.The quality of life of HIV infected patients with End stage renal disease is also improved after transplantation.

Recent evidence showed acute rejection due to interaction between boosted protease inhibitors regime and immunosuppressive drugs. Other issue is CNIs causing toxicity due to their higher blood levels as inhibited by cytochrome P450 3A4, [boosted –PI]. Alternate approach is to use non-nucleoside reverse transcriptase inhibitors [NNRTIs] with CNIs. With HAART therapy, monitoring of opportunistic infections, and knowing drug interactions, transplantation outcomes can be as good in HIV –positive patients as in HIV-negative.

2.11.8 Viral infections and rejection in kidney transplantation

Rejection of kidney allograft seen with viral infections. Studies showed 72% rejection with

CMV infection and 17% without any virus infection. Different mechanisms are involved in rejection process, including HLA class I –antigen specific T-cells, endothelial cell injury, release of proinflammatory cytokines , along with reduction in immunosuppressive drugs by physician in an infection. In more susceptible patients, use of [mTORi] with or without CNI decreased the incidence of CMV and BK polyoma infection.

2.11.9 Viral Infections and malignancy in kidney transplantation

In late post-tranplant period viral infections increases risk of malignancy. Common viruses,EBV, HPV,HTLV 1,HHV8, HBV, HCV , and polyoma have been known to cause urothelial malignancies in kidney transplant patients. Use of TORi can inhibit viral replication and malignant transformation.

The article is of particular importance to our kidney transplantation practice.

CMV risk stratification is done in every recipient pre-transplantion and duration of prophylaxis or no prophylaxis is decided based upon it, this is in accordance with the article recommendations and the AST guidelines for CMV 2019.

We use the hybrid strategy of initial prophylaxis for the specified duration and then pre emptive monitoring till the end of first year.

99 percent of our kidney transplant recipients are intermediate risk CMV. One practice difference because of a resource limited country is that for our intermediate risk patients (CMVD+ Recipient IgG+) we administer lower dose valganciclovir 450mg daily for a duration of 3 months. I am unaware of any data of a higher dose or longer duration prevents CMV reactivation in such scenario.

For high risk CMV status a considerable evidence also exists for a lower dose ie 450mg daily for a duration of 6 months.[8,9,10].

The approach is cost effective and we have less of a leukopenia issue which occurs with a higher dose of valcyte and MMF combination. I have been doing this for 2 years at my program with good success. We use lower dose of MMF in our program and most low immunological risk patients are on single Tacrolimus monotherapy,so incidence of CMV and BK is negligible. Researchers may debate that low dose valgancyclovir can increase CMV resistance.[11,12].

After prophylaxis is finished we do pre emptive monitoring at 4 or 7 months, then every 3 months for the first year because of resource constraints and cost of CMV PCR DNA.

Regarding treatment of CMV we use gancyclovir for 21 days or when two PCR at 1 week interval is negative in addition to clinical resolution of the disease. We don't use secondary prophylaxis.

Regarding diagnosis of CMV, we have all facilities including, PCR, all modalities of radiology and great histopathology services, mentioned in the the article and new AST 2019 guidelines.

Regarding resistant CMV we cannot check for mutations when we are faced with a suspected case, so the best we can do is increase gancyclovir dose to 10mg/kg daily and add renally adjusted foscarnet.

Upon detection of CMV viremia we stop MMF(mycophenolate moefitil) and rarely start again unless it is a high immunological risk recipient or previously a rejector.

BK surveillance is almost similar to the article with few differences.

BK viremia is checked rather viruria, because of the availability, although it makes much sense to catch at a rising viruria level, rather to wait for it to appear in the serum.

But it is known that half of the high levels of viruria may not transform into viremia. Secondly people do not advise intervention at the viruric level.

BK PCR is checked in blood every month for first nine months, thereafter every three months for the first two years and then checked only in paediatric population.

We have the feeling that after two years after kidney transplantation, recipients are on smaller doses of immunosuppressive medications and as described above the low immunological risk are on a tacrolimus monotherpy, and checking for BK is neither cost effective nor helpful.

An argument can be made as the renal functions starts to reduce, MMF (mycophenolate)

clearances can be reduced increasing the risk of BK viremia/ nephropathy. When BK viremia is detected depending upon the room of immunosuppression reduction in that specific patient, MMF is reduced or stopped and almost rarely started. This is in some variation to guidelines as they recommend reduction of immunosuppression if the BK viremia is greater than 1000 for 3 weeks. After detection of BK viremia we monitor BK by serum PCR every two weeks.

If the BK viremia is not decreasing we reduce the dose of tacrolimus to keep the levels between 3-4. I am aware that in the initial period Post Transplantation the incidence of rejection increases when tacrolimus levels are less than 5.

Biopsy is not done when the renal functions are normal, and also in case of very high BK viral load despite increased serum creatinine.

We do biopsy when in spite of reducing immunosuppression, BK viremia is decreasing ,but creatinine is increasing so we are not sure, and want to rule out acute rejection which can occur as a result of reduction in immunosuppression.

In such a scenario where we encounter BK and rejection together, since the signal is gamma interferon we use steroids and IVIG.

In resistant BK nephropathy cases,we use IVIG which is not responding to reduction in immunosuppression. No RCT'S exist demonstrating the efficacy of leflunomide,cidofovir or quinolones.

EBV risk stratification is done for kidney transplant recipients but monitoring for BK viremia is only done in paediatric population. In high risk EBV recipients EBVD+R-, a thorough evaluation for symptomatic PTLD is done in every clinic encounter including examination for lymphadenopathy and hepatosplenomegaly.

Regarding EBV/PTLD management we stop mycophenolate upon detection of PTLD and change tacrolimus to everolimus. Whenever using everolimus we make sure there is no proteinuria..

Intuitively, one might expect that PTLD = over-immunosuppression and immunosuppression can be indefinitely withheld indefinitely in PTLD patients without incurring rejection. However, this type of post-PTLD allograft "tolerance" is not invariable. In many patients, immune responsiveness is restored partially or completely at an unpredictable time post-PTLD. Thus, it is better to use (at least less intense) anti-rejection therapy.

The timing and intensity of reintroduction of such therapy is purely a "judgment call" based on an assessment of the aggressiveness of the PTLD, the completeness/duration of remission of the malignancy and the baseline risk factors for rejection (HLA-match,, DSA, recent rejections, living vs. deceased donor, renal function, proteinuria, time since transplant, etc.).

One faces a similar decision also in patients with other types of post-transplant malignancies and infections (especially BK virus infection after reduced immunosuppression has eradicated viremia).

In relation to hepatitis B, all kidney transplant candidates and donors are checked for hepatitis B, surface antigen(HBsag) and hepb core antibody(hbcigg).

The one's with HBSag positive or hep B core positive, will have HBV DNA checked. If HBVDNA comes positive, delta virus is checked and entacavir or tenofovir is started.

Then we do liver evaluation with ultrasound, fibroscan/shearwave elastography and do noninvasive scoring by APRI(albumin to platelet ratio index) and FIB4 ,indices to differentiate between cirrhotic vs non cirrhotic.

Although these APRI, FIB4 scoring system, shear wave elastography, fibroscans are not validated in ESRD population, they are still employed as the initial noninvasive tools.

Shear wave elastography/fibroscan becomes an issue in our ESRD population, as patients are inadequately dialysed and livers are congested giving falsely high stiffness on fibroscan. Similarly because of inadequate dialysis the patients have ascites causing difficulty in fibrosis assessment by fibroscan.

In doubtful cases liver biopsy is performed. We also make sure that patients are adequately dialysed before biopsy, otherwise they bleed.

When fibrosis score(metavir) is up to F3 only kidney transplantation is planned.

Before kidney transplantation we make sure patients are on entecavir/tenofovir and HBV DNA is below the detection limit in serum.

Then these patients continue life long entecavir or tenofovir.HBV DNA is checked every 3 months post transplant in the first year and then we do yearly.

When the fibrosis score (metavir) is F4 we then rule out portal HTN, by checking the hepatic to portal vein gradient through a transjugular catheter.

If the hepatic to portal vein gradient is greater than 10 indicating portal HTN,SLK (simultaneous liver kidney transplantation) is planned and 2 donors sorted out.

When the gradient is less than 10 only kidney transplantation is performed.

In our program we don't accept hepatitis B surface antigen positive donors. But it is possible with the following protocol

Make sure the recipient is immunised and anti hbs titres are protective.

In case of sub therapeutic or negative titres, hepatitis b globulin should be administered at the time of transplant surgery.

In case of high titres no need of antivirals postop. In case of low titres antivirals should be given for 1 year.

Hepatitis B living donor should only be acceptable if HBV DNA is undetectable in serum. Postransplant HBV DNA titres will be monitored every 3 months for the first year. Hepatitis B core positive donors can be considered if HBV DNA is negative and recipient antihbs titre is greater than 10.

All kidney transplant recipients and donors are first checked for hepatitis C antibody(antiHCV).

In AntiHCV positive we perform PCR for HCV RNA and if it is positive genotyping is also assessed.

Liver evaluation is done exactly in the same fashion as is done for hepatitis B.

3. CONCLUSION

Direct antiviral agents are started following transplantation in HCV viremic recipients. Kidney transplant recipients who have significant transaminitis before transplantation, DAA are started before transplantation because anaesthesia are uncomfortable with ALT' more than 100.

Hepatitis C positive donors are acceptable if they are PCR negative.

PCR positive donors are first treated and SVR achieved before considering him or her as a donor for HCV- recipient.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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