INFECTIONS AND VIRAL RELATED CANCERS IN THE RENAL TRANSPLANT RECIPIENT

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1. ABSTRACT

Infection and infection related cancers are becoming the major cause of death with a functioning transplant now that cardiovascular risk is better managed. The commonest infection is cytomegalovirus (CMV), which can be contained by appropriate pre-emptive or prophylactic therapy. A recent addition to the list of important viral infections is BK virus which can cause graft loss from an interstitial nephritis. Both Herpes simplex and Varicella zoster can be devastating in the immuno-compromised patient if the recipient is immunologically naïve (antibody negative). Bacterial infections remain significant but are more readily diagnosed and usually easily treated except for the increasing problem of highly resistant hospital strains.. In certain areas Mycobacterium tuberculosis is increasingly important. Fungal and parasitic infections are in the main limited to certain geographical areas. It is vital that the transplant community works closely with the Virologist and Bacteriologist to make best use of the latest diagnostic techniques and anti-microbial agents. Prophylaxis which includes pre-transplant vaccination as well as post grafting administration of antimicrobials is of crucial importance. It is clear that without the parallel progress in microbiology, the modern immunosuppressive regimes could not have been safely introduced.

2. INTRODUCTION

Renal transplant patients are liable to develop a range of infections and cancers similar to that seen in patients with Human immunodeficiency virus (HIV) (table 1).

TABLE 1: MAJOR POST TRANSPLANT OPPORTUNISTIC INFECTIONS

VIRUSES		BACTERIA
Herpes viruses		Resistant Hospital micro organisms
HIV		Brucella
HTLV 1		Listeria
Hepatitis B & C		MTB
Adenovirus		Syphillis
		Contamination of perfusate
Rare:	Rabies	Bacteraemia
	LCMV	
	WNV	Urinary tract infection
Respiratory viruses		
FUNGI		**PARASITES**
Candida		Toxoplasma gondii (heart)
Endemic:	Histoplasma	Trypanosoma cruzi (endemic areas)
	Coccidioides	
Cryptococcus		
(Important in lung transplantation)		
NB: Deep donor fungal infections		

Modern immunosuppressive regimes effectively paralyse the T helper cell and open the door to a variety of infections [1]. Traditionally [2] infections are divided into early (month 1), intermediate (month 1 – 6) and late (> 6 months) post grafting. Early infections are often related to the procedure itself for example wound, line, urinary catheter related and chest. Unusual infections in the early period may be due to donor transmitted infections (table 2) which may be a primary infection (i.e. a naïve host) e.g. Varicella zoster (VZV), Herpes simplex virus (HSV e.t.c): Other unusual early opportunistic infections may represent a particularly high environment risk e.g. Aspergillus from hospital building works.

TABLE 2: IMPORTANT DONOR DERIVED INFECTIONS

Inhibition of dendritic cell function	
Block protosome	
Block transporter of antigenic peptides	
Divert HLA – ag complex to cytosol	
Virokines: ie6, ili0 Iℓ - 6, Iℓ 10	
Viral oncogenes	
Antiapoptotic proteins	
Cytokine receptors:	Soluble Signalling Constitutively active Non-signalling (act as a sump)
Reduced HLA expression/pseudo HLA	

During months 1 to 6 the effects of the immunosuppression are maximal and the main array of opportunistic infections may be seen. After 6 months, immunosuppression is generally reduced and the infection risk is similarly reduced but not down to normal. Patients who have had potent depleting antibodies or whose graft function is poor remain at a much increased risk for longer.

3. VIRAL INFECTIONS

i. Cytomegalovirus (CMV) is the main post-transplant infection. CMV is so called as it is a large and complex virus with over 250 genes. Many of these genes are capable of subverting the host immune response and explain why CMV and the other herpes DNA viruses are so successful (table 3). The main risk factors for CMV and for most other viruses are viral load [3] and the total burden of immunosuppression (table 4).

TABLE 3 VIRAL STRATEGIES FOR IMMUNE EVASION

- (Viral load D+/R- < D+/R- < D-/R+)
- Total burden of immunosuppression
  E.g. Depleting antibodies
  MMF
- ← Lack of functioning viral specific CTL

TABLE 4: RISK FACTORS FOR CMV

Common major:	Retinitis
	Pneumonitis
	GI tract – colitis
	Hepatitis
	Cytopaenias
	CMV syndrome
Uncommon/minor:	Almost any tissue/organ
	Vascular damage (TMA)
	Nephropathy: Glomerulitis
	Interstitial Nephritis
	CNS
	Arthritis
	Skin rashes
	Pseudolymphoma

CMV has both direct (cytopathic and lytic) effects (table 5) and indirect effects [4] which are much more subtle (table 6 and 7). Of the two equally effective management strategies for CMV (universal prophylaxis or targeted pre-emptive therapy), it is not clear which is the more effective at preventing the indirect effects [5,6]

TABLE 5: DIRECT EFFECTS OF CMV

Immune modulation:	Superimposed opportunistic infections
	Increased cancer risk
Specific viral proteins:	
	Inhibition of apoptosis

Resistance to NK cells
Inactivation of p53
Expression proto-oncogenes
Angiogenesis
Induction of scavenger receptors
Stimulation of Iℓ – 1 production
Binding of platelets to endothelial cells
Expression of adhesion molecules
Expression of G-coupled receptors
Inflammation (Iℓ - 1, MCP 1, RANTES, Iℓ - 8, Iℓ - 6)

TABLE 6: PATHOGENIC MECHANISMS FOR THE INDIRECT EFFECTS OF CMV

Opportunistic infections:	Fungi (PCP)	
Viral (BKV, EBV)		
Bacterial		
Vascular damage:	TMA	
		CAN
		Accelerated Atherosclerosis
New onset diabetes after transplantation		
Cancer:	PTLD	
		KS
Rejection:	Acute	
	Chronic	
Epidemiological: Reduced patient and graft survival		

TABLE 7: INDIRECT CLINICAL EFFECTS OF CMV

- 75% recipients sero-positive for BKV antibody
- 50% renal transplants reactivate BKV and excrete virus (urine decoy cells)
- 5% viral replication in blood
  (PCR positive)
- 1 – 5% overt nephropathy
  ≤ 50% lose graft
  25% permanent loss of GFR

Of increasing concern is late CMV that may follow three months of prophylaxis. Valgancyclovir (VGCV) is effective both for therapy and prophylaxis (ref 7). Both management strategies should be supported by regular estimations of the quantitative PCR for CMV or CMV antigen in the blood. Treatment should not be stopped until two consecutive negative PCRs have been obtained. Resistant CMV is rare in renal transplants but can be managed by Foscanet or Cidofovir. Newer agents such as Maribavir are shortly to be available. Supplementary intravenous immunoglobulin (IVIG) may be of value in severe or persistent disease.

ii. BK virus (BKV) is another DNA virus which persists in the host. It may be reactivated following transplantation and can be detected in the urine by cytology for decoy cells or PCR [8]. Reactivation of BKV does not necessarily mean that graft damage (so called BKV nephropathy) will occur

and this event needs confirmation by biopsy (table 8) [9]. Regular monitoring (table 9) is important and early detection may improve outcome [10].

TABLE 8: BKV REACTIVATION AND NEPHROPATHY

Year 1 – 2	Months 1, 3, 3 monthly
Year 3 – 6	Annual
At every episode of graft dysfunction	
Before every graft biopsy	
If positive urine:	Repeat monthly Check blood for PCR (> 10,000 c/ml consider biopsy)

TABLE 9: URINE SCREENING FOR BKV

D+ / R –
HLA mismatch
Number of treated rejections
Total burden of immunosuppression
Tacrolimus > Cyclosporin A
MMF > Azathioprine
CMV D+
Delayed graft function
Stent
Prolonged cold ischaemic time
Older age
Female gender
Absence of HLA – 7
TGFβ polymorphism (G 915c)

It is currently felt that the main risk factor for BK virus nephropathy is the use of more potent immunosuppressive agents but other factors may be important (table 10). Management consists of immunosuppression dose reduction (ISDR) and possibly anti-viral agents such as Cidofovir or Leflunamide. IVIG may be of value if rejection occurs in the context of reduced immunosuppression. If graft fibrosis is extensive, conversion to sirolimus may be of value. If BKV nephropathy is advanced and well established approximately half the patients will ultimately lose their grafts.

TABLE 10: RISK FACTORS FOR BKVN

VIRUS	CANCER
EBV (HHV4)	PTLD
HPV	SCC (Skin, upper GI) (Anogenital cancer)
KSV (HHV8)	Kaposi's sarcoma
HBV/HCV	Hepatocellular cancer

MC polyoma virus	Merkel cell cancer
HTLV1	Leukaemia

iii. Other viruses: In some respects patients behave like sentinel chickens and develop virus infections earlier and more severely than the general population and thus for example may provide early warning of an influenza outbreak. Respiratory virus infections are common [11] and can be severe (table 11) in renal transplant patients. Secondary bacterial infection is common. Early use of naso-pharyngeal aspiration (NPA) and examination of the sample by PCR for the respiratory viruses can give a rapid diagnosis. Patients with abnormal chest x-rays or those who desaturate on exercise may need admission and bronchoscopy. Rare outbreaks of unusual viruses are reported in the transplant community for example West-Nile virus, Lymphochoriomeningitis and rabies. It is important to remember that a primary infection (naïve host) with HSV, VZV, measles and other viruses can produce devastating disease in renal transplant patients.

4 Viral related cancers

i. General :

Several viruses encountered following transplantation have an oncogenic potential (table 12) [12]. In some respects these viral driven cancers initially behave more like infections in their early natural history as regression may occur with immunosuppression dose reduction (ISDR). CMV plays an important role in increasing risk (see indirect effects of CMV table 7).

ii. Post transplant lymphoproliferative disorder (PTLD)

Some include all lymphomas and lymphoma-like conditions as PTLD and not just the narrower concept of Epstein Barr virus (EBV) driven B cell lymphomas. Classification is complex (table 13) and it can sometimes be difficult to fit a particular case into the scheme [13]. Nevertheless PTLD is common (table 14) and an important complication post transplant. Despite current optimal management there is still an approximately 40% mortality. Risk factors include a primary EBV infection (viral load) and the total burden of immunosuppression (blockade of EBV-specific CTLs). Presentation is so varied that clinical awareness is important (table 15). It is vital to evaluate fully the tumour with immuno-phenotyping [15] and staging with PET scanning [16]. Management should be a combined approach with an experienced haematologist/oncologist and transplant physician. Management is complex (figure 1) but in the first instance, ISDR with or without the early introduction of Rituximab is the usual first step in non life-threatening disease [17]. It is important to withdraw the anti-proliferative immunosuppressive agents first so that if conventional chemotherapy is required, the bone marrow will be able to withstand the medication. Specific cytotoxic lymphocytes (CTL) have been produced and can be effective but are currently of very limited availability. Re-transplantation after cure appears safe. Antiviral agents have no role in therapy.

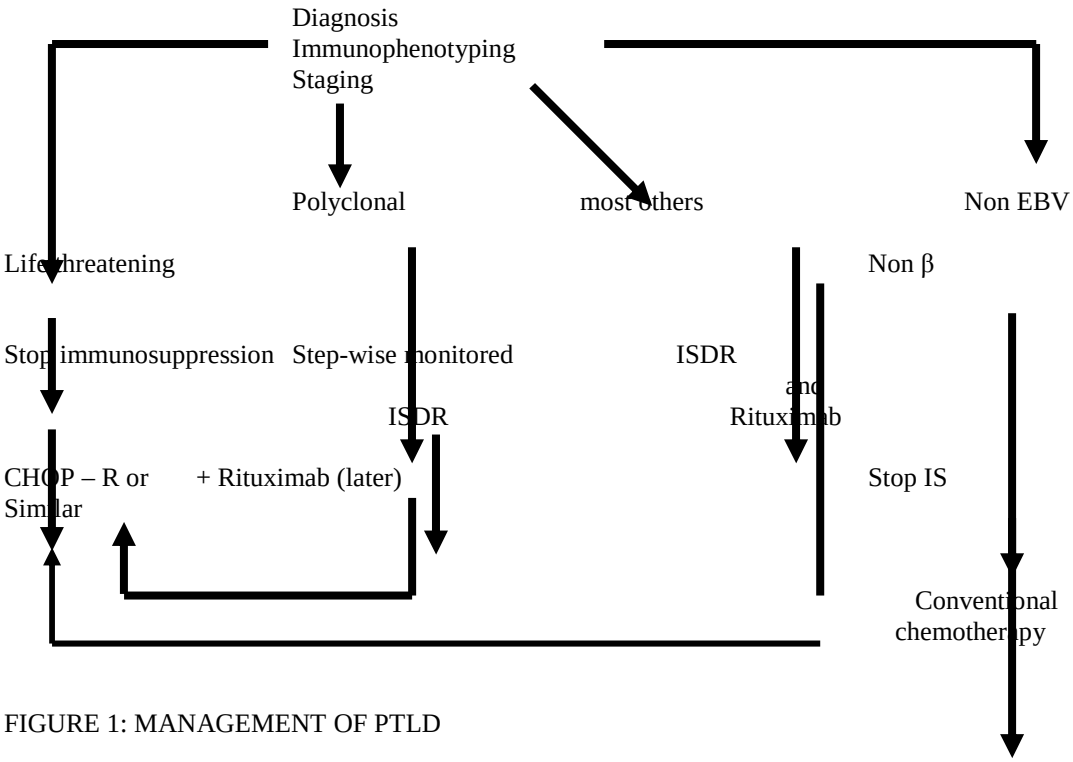


FIGURE 1: MANAGEMENT OF PTLD

iii. Kaposis' Sarcoma

Kaposi's sarcoma (KS) is driven by another herpes virus (HHV8 or human herpes virus 8) the so called Kaposi's sarcoma virus [18]. KS is a very vascular tumour and recently the anti-angiogenic properties of Sirolimus have been utilised to inhibit the tumour without an unacceptable risk of precipitating acute rejection were immunosuppression to be withdrawn [19,20]. Anti-viral agents are not effective. Local excision and radiotherapy may be effective in localised disease. Chemotherapy with bleomycin or doxorubicin can be effective and is remarkably well tolerated [21]. KS is somewhat geographically limited (the Mediterranean littoral and the Arab peninsula) and the risk factors as are similar to those for PTLD. A full investigation and staging are important as 40% of cases have visceral involvement. Retransplantation was not possible until the advent of sirolimus but experience is still very limited.

iv. Human Papilloma Virus (HPV) and squamous cell cancer(SCC)

a) Skin cancers

Squamous cell cancer of the skin is extremely common in sun exposed Caucasian patients of skin types 1 & 2 following transplantation (ref 22). The incidence can reach 80% some 20 years post transplant in the white Australian transplant population. The three main aetiological factors are ultraviolet light, immunosuppression and HPV. Pharmacongenetics may play a role in as much as some patients do not metabolize azathioprine efficiently [23] and there are polymorphisms of glutathione-S-transferase which are associated with disease.

Azathioprine enhances the adverse effects of UV light on the skin. It is a vital part of long term management to examine the whole of the integument and anogenital areas on annual basis. Management should include ISDR. Currently an international multi centre trial is in progress looking at the effects of conversion from conventional immunosuppression to Sirolimus. The help of an experienced Dermatologist is essential as clinical diagnosis is often difficult and biopsies are frequently needed. Topical treatment can usually control the condition but it is important to remember the SCCs represent a field defect in the skin and recurrence is extremely common.

b) Anogenital cancers

Anogenital cancers are clearly related to specific types of HPV (16 and 18). They occur earlier, are often more multifocal and metastasize more commonly in the immunocompromised patient [24]. Regular surveillance is a key to early diagnosis and good management. ISDR is usually undertaken. Local treatment is along conventional lines and may control disease adequately. Sometimes quite extensive surgery is required. Topical cidofovir can be effective.

v Merkel Cell Cancer (MCC):

Very recently a new virus has been implicated in this rare post transplant tumour (Merkel cell polyoma virus). Lesions appear as erythematous nodules on the head and neck. About half the patients develop lymph node involvement or metastasis [25]. Prognosis is poor with about 40% survival at 2 years. Immunosuppression should be reduced. Local excision with removal of affected nodes is the usual first step to treatment. With widespread disease, treatment with chemotherapy is undertaken.

vi Hepatocellular Cancer (HCC)

Both hepatitis B and hepatitis C viruses are associated with hepatocellular cancer (HCC) in renal transplant patients [26]. Early diagnosis is difficult (monitoring with alpha-feto protein and annual liver ultrasounds may help in those at risk). Treatment is not very effective. Therapeutic liver transplantation could be considered if disease is well localised.

5. BACTERIAL INFECTION

The commonest bacterial infection post transplantation is urinary tract infection (UTI) (ref 27). UTIs are the commonest cause of bacteraemia/septicaemia. It is important to recognise that UTIs probably including asymptomatic bacteruria can be associated with acute bacterial pyelonephritis (particularly in the presence of reflux to the graft or bladder dysfunction). These upper tract infections can lead to severe graft scarring and even allograft loss. Long term prophylactic antibiotics may reduce scarring [28].

Community acquired pneumonias are also very common in the transplant population (many are viral infections). Most of the bacterial chest infections will be due to Strep pneumoniae as in the general community. Other more serious bacterial pneumonias may occur in the transplant population (table 16). Aggressive and rapid investigation is required to find the organism and choose the most appropriate therapy.

Mycobacteria tuberculosis (MTB) is still a common infection in the transplant community and reactivation is common after immunosuppression [29, 30]. Clinical awareness is crucial. Treatment is along conventional lines but the transplant physician and respiratory physician will need to liaise carefully over the important drug interactions. Patients on rifampicin usually need a doubling of their steroid dose and up to a threefold increase in their calcineurin inhibitor. Bacterial (and fungal) contamination of the graft at procurement should not be forgotten. Preservation fluid should always be cultured and if positive, appropriate antibiotic prescribed. Fatal haemorrhage from a mycotic aneurysm complicates suture line infection.

6. FUNGAL AND PARASITIC INFECTIONS

A detailed account of fungal and parasitic infections is beyond the scope of this review. The reader is referred to several excellent reviews [29,30,31].
Fungal infections are usually due to Candida, Aspergillus, Cryptococcus or Mucor unless there is a particular geographically defined spectrum of fungal infections in the community (table 17).

TABLE 17: POST TRANSPLANT FUNGAL INFECTIONS
ALLOGRAFT DYSFUNCTION

Prolonged / repeated surgery
Multiple acute rejection episodes (excessive steroids)
Augmented immunosuppression
CMV, HCV
Intensive care unit
Broad spectrum antibiotics
Donor fungaemia
Prior fungal infection (reactivation)
Prolonged retention of lines, catheters, drains e.t.c
Environmental exposure
Marijuana use
Diabetes mellitus
Malnutrition
Granulocytopaenia
Hypogammaglobulinaemia

A particular problem is contamination of the donor organ/preservation fluid with fungi which can lead to a catastrophic haemorrhage from a mycotic aneurysm [31]. Awareness of the risk factors for fungal infections will help select patients for appropriate investigations (table 18).

TABLE 18: RISK FACTORS FOR FUNGAL INFECTIONS

ACUTE SYSTEMIC ILLNESS
Leismaniasis *
Trypanosomiasis *
Toxoplasmosis *
Babesiosis *
Strongyloides*

LOCALISED INFECTION
Cryptosporidium
Microsporidium *
Strongyloides *
Ascaris
Amoebiasis *
Balantidiasis
Giardiasis
Trichuriasis

Cyclospora
Schistosomiasis
Trypanosomiasis *

* POTENTIAL FOR WIDESPREAD DISSEMINATION

Serum galactomannan may be helpful and serum or CSF for cryptococcal antigen (CRAG) can be diagnostic. The newer antifungal agents have made treatment easier (e.g. Posaconazole, Voriconazole, Caspofungin, Micofungin). Although over 300 parasitic infections can affect man, only about 15 are of particular importance in the transplant population (table 19). Some have the potential for systemic spread [33]. Many are geographically defined. With the increase in transplant tourism and travel in general, it is important to consider these more exotic infections in the transplant community.

TABLE 19: PARASITIC INFECTIONS POST TRANSPLANTATION

PRETRANSPLANT (PRE DIALYSIS IF POSSIBLE)VACCINATION

Routine childhood/adolescence vaccinations e.g.

Polio BCG MMR
DPT Meningtitis C
Pneumococcus Haemophilus (HIB)

HBV
HAV (if liver damage)
Influenza (annual)
VZV
Meningococcal C (if < 25 years, not vaccinated)
Booster HIB
Pneumococcus (≥ 5 yr)
Rubella (if child bearing potential)

POST TRANSPLANT VACCINATION

No living or attenuated vaccines!
The following vaccines are contraindicated
Mumps
Rubella
Measles
BCG
Live oral Polio (alternative available)
VZV
Yellow fever
Rotavirus
Oral Typhoid (alternative available)

7. PREVENTION

Neither donor nor recipient should be put forward for transplantation in the presence of undiagnosed or untreated infection. Screening is extremely important. Where possible, the recipient should be fully investigated and vaccinations kept up to date. Vaccination should ideally be undertaken before dialysis in order to ensure a good response (table 20). As a general principle living or attenuated vaccines should not be given to immunosuppressed patients [34].

TABLE 20 VACCINATIONS

ALL	SELECTED
Wound: Augmentin	Isonaizid
PCP: Co-trimoxazole (listeria, Toxoplasmosis, Nocardia, UTI)	HSV Ab Neg: VALACV
CMV: Universal prophylaxis Or Pre-emptive therapy	HBV: Antivirals
	Syphillis: Benzathine Penicillin
Fungal: Nystatin mouth wash	Geographical: e.g. Histoplasmosis: Itraconazole Trypanosomiasis: Nifurtimox
UTI (recurrent) Rotating antibiotic	Past cryptococcus: Fluconazol

Most Transplant Centres recommend a 3 day antibiotic regime to reduce the risk of wound infections. Three months Co-trimoxazole is given in low dose and the strategy has effectively eradicated Pneumocystis jiroveci as an important clinical problem. Either universal prophylaxis or pre-emptive therapy for CMV using valgancyclovir (VGCV) is mandatory [35]. Most will still give isonaizid to patients at particular risk of reactivation of MTB [36]. Vaccines for EBV, HPV and CMV are in development and will hopefully be of benefit to recipients of solid organ transplant patients in the future.

REFERENCES

1. Fishman J.A. Infection in solid organ transplant recipients N. Engl. J. Med 2007 357 2601 – 14

2. Rubin R.H and Young L.S
Clinical approach to infection in the compromised host, 3rd Edition 1994 Plenum

Medical, New York

3. Mattes F.M, Hainsworth E.G, Hassan-Walker A.F et al

Kinetics of cytomegalovirus load decrease in solid organ transplant recipients after

pre-emptive therapy with valganciclovir

J. Infectious disease 2005 191 (1) 89 – 92

4. Paya C. V.

Indirect effects of CMV in the solid organ recipient

Transplant infectious disease 1999 supplement 1, 8 – 12

5. Hart G.D and Paya C.V

Prophylaxis for CMV should now replace pre-emptive therapy in solid organ transplantation.

Rev. Medical Virol 2001 11, 83 – 6

6. Emery V.C

Prophylaxis for CMV should not now replace pre-emptive therapy in solid organ transplantation

Rev Med. Virology 2001 11 73 – 81

7. Sun H – Y, Wagener MM, Singh N.

Prevention of post transplant cytomegalovirus disease and related outcomes with valganciclovir: A systematic review

AM J Transpl. 2008 8 2111 - 2118

8. Dall A, Hariharan S

BK virus nephritis after renal transplantation

Clin J AM Soc. Nephrology 2008 3 568 – 575

9. Blanckaert and DeVriese An S

Current recommendation for diagnosis and management of polyoma BK virus nephropathy in renal transplant recipients

Nephrology Dialysis Transplant. 2006 21 3364 – 3367

10. Vasudev B. Hariharan S., Hussain S.A, Zhu Y – R, Bresnahan B.A, Cohen E.P.

BK Virus Nephritis: Risk Factors, Timing and Outcome in Renal Transplant Recipients

Kid. Int. 2005 68 1834 – 1839

11. Chien J.W and Johnson J.L

Viral pneumonias: Infection in the immunocompromised

Postgraduate Medicine 2000 107 (2)

12. Talbot S.J, Crawford D.H

Viruses and Tumours – An update

Eur. J. Cancer 2004 40 1998 – 2005

13. Nalesnik MA

Clinico-pathologic characteristics of post-transplant lymphoproliferative disorders

Rec. Res. Cancer Ros 2002 159 9 – 18

14. Lim WH, Russ GR, Coates PTH

Review of Epstein-Barr virus and post-transplant lymphoproliferative disorder post-solid organ transplantation

Nephrology 2006 11 355 – 366

15. Capello D, Rossi Davide, Gaidano G.

Post- transplant lymphoproliferative disorder: molecular basis of disease histogenesis and pathogenesis

Hematol Oncol 2005 23 61 – 67

16. Scarsbrook AF, Warakaulle DR, Dattani M, Traill Z

Post-transplant lymphoproliferative disorder: The spectrum of imaging appearances

Clin Radiol 2005 60 47 – 55

17. Taylor AL, Marcus R, Bradley JA

Post-transplant lymphoproliferative disorder (PTLD) after solid organ transplantation

Crit Rev. Oncology/Haematology 2005 56 155 – 167

18. Noy A

Update in Kaposi Sarcoma

Curr opin Oncol 2003 15 379 – 381

19. Dittmer DP, Krown S.E

Targeted Therapy for Kaposi's Sarcoma and Kaposi's Sarcoma-associated Herpes

virus

Current opinion Oncology 2007 19 452 – 457

20. Stallone G, Schena A, Infante B et al

Sirolimus for Kaposi's sarcoma in Renal-Transplant Recipients

N. Engl. J Med 2005 352 1317 – 23

21. Antman K and Chang Y

Kaposi's Sarcoma

N. Engl. J. Med. 2000 342 1027 – 1038

22. Euvrard SE, Kanitakis J, Claudy A
Skin cancer after organ transplantation
N. Engl. J. Med. 2003 348 1681 – 91

23. Ulrich C, Stockfleth E
Azathioprine, UV light and skin cancer in organ transplant recipients – Do we have an answer?
Nephrol, Dial Transpl 2007 22 1027 – 29

24. Penn I
Cancers of the anogenital region in renal transplant recipients. Analysis of 65 cases
Cancer 1986 58 611 – 16

25. Penn I, First MR.
Merkel's cell carcinoma in organ recipients
Transplantation 1999 68 1717 – 1721

26. Fornairon S, Pol S, Legendre C, Carnot F et al
The long term virologic and pathologic impact of renal transplantation on chronic hepatitis B infection
Transplantation 1996 62 (2) 297 – 299

27. De Souza RM and Olsburgh J
Urinary tract infection in the renal transplant patient
Nature clinical practice 2008 4 252 – 264

28. Dupont PJ, Psimenou E, Lord R, Buscombe JR, Hilson AJ, Sweny P
Late recurrent urinary tract infections may produce renal allograft scarring even in the absence of symptom or vesicoureteric reflux
Transpl. 2007 84 352 – 355

29. Aguado JM, Herrero JA, Gavalda J et al
Clinical presentation and outcome of tuberculosis in kidney liver and heart transplant recipients in Spain.
Transplantation 1997 63 1278 – 86

30. Higgins RM, Cahn AP, Porter D et al
Mycobacterial infections after renal transplantation
Q.J. Med 1991 78 (286) 145 – 53

31. Matignon M, Botterel F, Audard V et al
Outcome of renal transplantation in eight patients with candida sp. contamination of preservation fluid
Am J. Transpl. 2008 8 697 – 700

32. Patterson TF
Advanced and challenges in management of invasive mycoses
Lancet 2005 316 1013 – 25

33. Barsoun R
Parasitic infections in transplant recipients
Nature clinical practice 2006 2 490 – 503

34. Green M, Avery RH, Preiksaitis J (Eds)
Guidelines for vaccination of solid organ transplant candidates and recipients
Am J Transpl. 2004 4 (suppl 10) 160 - 163

35. Marty FM, Rubin RH
The prevention of infection post-transplant: The role of prophylaxis, prevention and empiric therapy
Transplant Int. 2006 19 2 – 11

36. John GT, Thomas PP, Thomas M, Jeyaseelan L, Jacobs CK, Shastry JC
A double – blind randomised controlled trial of primary Isonaizid prophylaxis in dialysis and transplantation
Transplantation 1994 57 1683 – 1684