INFECTIONS AND VIRAL RELATED CANCERS IN THE RENAL TRANSPLANT RECIPIENT

Name: Dr Paul Sweny MD FRCP
Affiliation: Consultant Nephrologist
Royal Free Hospital London NW3 2QG, UK

Conflicts of interests: Dr Sweny has attended conferences, served on Advisory Boards and given lectures and seminars sponsored by Roche, Novartis, Wyeth and Astellas.

Contact: Renal Unit, Royal Free Hospital, London NW3 2QG
Email: paul.sweny@btinternet.com
Telephone: 07979770994

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CONTENTS

1. Abstract
2. Introduction
3. i. CMV (Cytomegalovirus)
   ii. BK virus (BKV)
   iii. Other viruses
4. Viral related cancers
   i. General
   ii. Post transplant lymphoproliferative disorder(PTLD)
   iii. Kaposi’s sarcoma(KS)
   iv. Squamous cell cancer(SCC) a) Skin b) Anogenital
   v. Merkel cell cancer
   vi. Hepatocellular cancer(HCC)
5. Bacterial infections
6. Fungal and parasitic infections
7. Prevention and prophylaxis
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

<table>
<thead>
<tr>
<th>VIRUSES</th>
<th>BACTERIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herpes viruses</td>
<td>Resistant Hospital micro organisms</td>
</tr>
<tr>
<td>HIV</td>
<td>Brucella</td>
</tr>
<tr>
<td>HTLV 1</td>
<td>Listeria</td>
</tr>
<tr>
<td>Hepatitis B &amp; C</td>
<td>MTB</td>
</tr>
<tr>
<td>Adenovirus</td>
<td>Syphilis</td>
</tr>
<tr>
<td></td>
<td>Contamination of perfusate</td>
</tr>
<tr>
<td>Rare: Rabies</td>
<td>Bacteraemia</td>
</tr>
<tr>
<td>LCMV</td>
<td>Urinary tract infection</td>
</tr>
<tr>
<td>WNV</td>
<td></td>
</tr>
</tbody>
</table>

Respiratory viruses

<table>
<thead>
<tr>
<th>FUNGI</th>
<th>PARASITES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candida</td>
<td>Toxoplasma gondii (heart)</td>
</tr>
<tr>
<td>Endemic:</td>
<td>Trypanosoma cruzi (endemic areas)</td>
</tr>
<tr>
<td>Coccidioides</td>
<td></td>
</tr>
</tbody>
</table>

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 If - 6, If 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 IFN-1 production
Binding of platelets to endothelial cells
Expression of adhesion molecules
Expression of G-coupled receptors
Inflammation (IFN-1, MCP 1, RANTES, IFN-8, IFN-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 Foscarnet 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**

<table>
<thead>
<tr>
<th>VIRUS</th>
<th>CANCER</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBV (HHV4)</td>
<td>PTLD</td>
</tr>
<tr>
<td>HPV</td>
<td>SCC (Skin, upper GI)</td>
</tr>
<tr>
<td></td>
<td>(Anogenital cancer)</td>
</tr>
<tr>
<td>KSV (HHV8)</td>
<td>Kaposi’s sarcoma</td>
</tr>
<tr>
<td>HBV/HCV</td>
<td>Hepatocellular cancer</td>
</tr>
</tbody>
</table>
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.
iii. Kaposi’s 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 pneumoniea 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
- Granulocytopenia
- 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

<table>
<thead>
<tr>
<th>ACUTE SYSTEMIC ILLNESS</th>
<th>LOCALISED INFECTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leishmaniasis *</td>
<td>Cryptosporidium</td>
</tr>
<tr>
<td>Trypanosomiiasis *</td>
<td>Microsporidium *</td>
</tr>
<tr>
<td>Toxoplasmosis *</td>
<td>Strongyloides *</td>
</tr>
<tr>
<td>Babesiosis *</td>
<td>Ascaris</td>
</tr>
<tr>
<td>Strongyloides*</td>
<td>Amoebiasis *</td>
</tr>
<tr>
<td></td>
<td>Balantidiasis</td>
</tr>
<tr>
<td></td>
<td>Giardiasis</td>
</tr>
<tr>
<td></td>
<td>Trichuriasis</td>
</tr>
</tbody>
</table>
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**

| Vaccine                        | 
|--------------------------------|----------------------------------|
| Polio                          | BCG                              |
| DPT                            | Meningitis 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

<table>
<thead>
<tr>
<th>ALL</th>
<th>SELECTED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wound: Augmentin</td>
<td>Isonaizid</td>
</tr>
<tr>
<td>PCP: Co-trimoxazole</td>
<td>HSV Ab Neg: VALACV</td>
</tr>
<tr>
<td>(listeria, Toxoplasmosis,</td>
<td></td>
</tr>
<tr>
<td>Nocardia, UTI)</td>
<td></td>
</tr>
<tr>
<td>CMV: Universal prophylaxis or Pre-emptive therapy</td>
<td>HBV: Antivirals</td>
</tr>
<tr>
<td>Fungal: Nystatin mouth wash</td>
<td>Geographical: e.g.</td>
</tr>
<tr>
<td>UTI (recurrent) Rotating antibiotic</td>
<td>Past cryptococcus: Fluconazol</td>
</tr>
</tbody>
</table>

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 valganciclovir (VGCV) is mandatory [35]. Most will still give isoniazid 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.

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