Infections after transplantation: Cases

Dr. Rhys Evans
Kidney Research UK Training Fellow
UCL Centre for Nephrology, UK
ISN Young Nephrologist Committee

www.theisn.org

Infections after transplantation: cases

Background

- Increasingly potent immunosuppression = reduced rejection, but increase susceptibility to opportunistic infections (+ cancer)

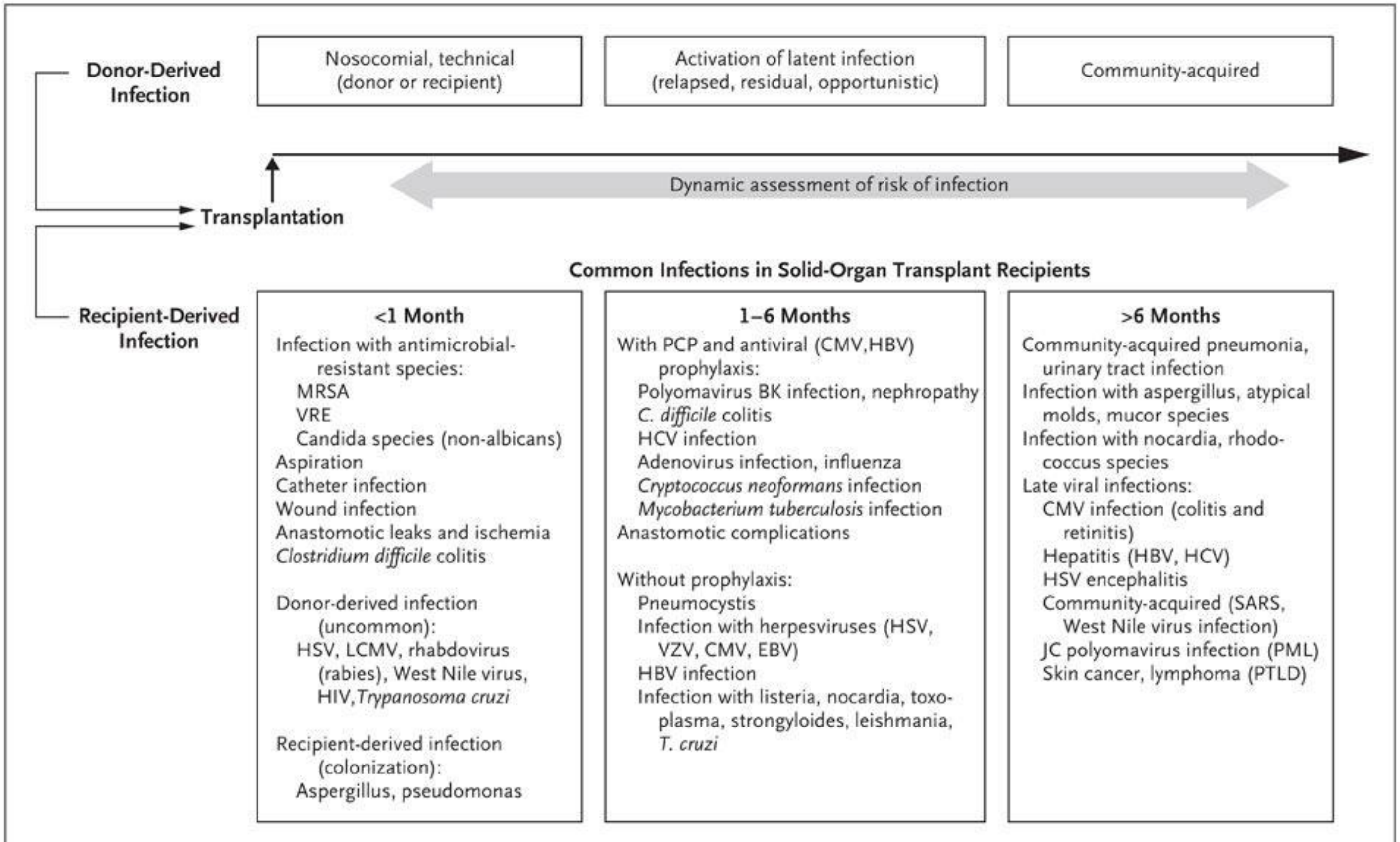
- Post transplant infection is a common cause of graft deterioration, morbidity and mortality

- Infections can be: Donor derived; Pre-existing in the recipient; Nosocomial; or Opportunistic

- Risk can be mitigated with:

Rigorous donor and recipient screening
Pre-transplant vaccination and treatment
Post transplant prophylaxis and
Early initiation of antimicrobial therapy

Timing of post transplant infections



Fishman et al, NEJM 2007

Case 1

- 43 year old gentleman, from Togo, political refugee in UK
- HIV

-diagnosed 2001, antiretroviral therapy since with good control

- ESRD

-presenting at end stage at time of HIV diagnosis

-large and bright kidneys with heavy proteinuria – presumed HIVAN (no biopsy due to HIV associated dysfibrinogenaemia)

-HD 2001 via tunnelled line for 6 months. MRSA bacteraemia

-PD 2001-2003. Pseudomonas peritonitis

-HD 2003-2011 via AVF

-Activated on transplant list 2005 (no live donors)

Stavudine/lamivudine/efavirenz

Tolerated trial of cyclosporin and MMF

Stavudine switched subsequently to abacavir

Case 1

- Cadaveric renal transplant 2011 (56 DBD)

-1,1,1 MM

-CMV +/+

-Basiliximab, cyclosporin, MMF 3g/day, prednisolone taper to 5mg over 2 weeks

-co-trimoxazole prophylaxis

-no valgancyclovir prophylaxis (unit protocol)

-primary graft function -> creatinine fallen to 145 by discharge

- 2 weeks after transplant

Pseudomonal UTI/graft dysfunction – i/v antibiotics

Low level CMV viraemia (3119 copies/ml) resolved with treatment dose valgancyclovir

MMF reduced to 1.5g/day

Back to creatinine baseline 140

Case 1

- 5 months post transplant creatinine rise to 170

-Biopsy: Banff 1A cellular rejection

-Methylprednisolone 500mg x3 then prednisolone 20mg, escalation of MMF to 2g/day, and increase in cyclosporin

- Further creatinine decline to 338 over next 10 days

-presumed untreated rejection

-further MP x3 and conversion cya -> tacrolimus

-prednisolone 20mg od, MMF 2g/day, tacrolimus

-creatinine fall to 179 over subsequent 2 weeks

Case 1

- 6 months post transplant

Progressive SOB

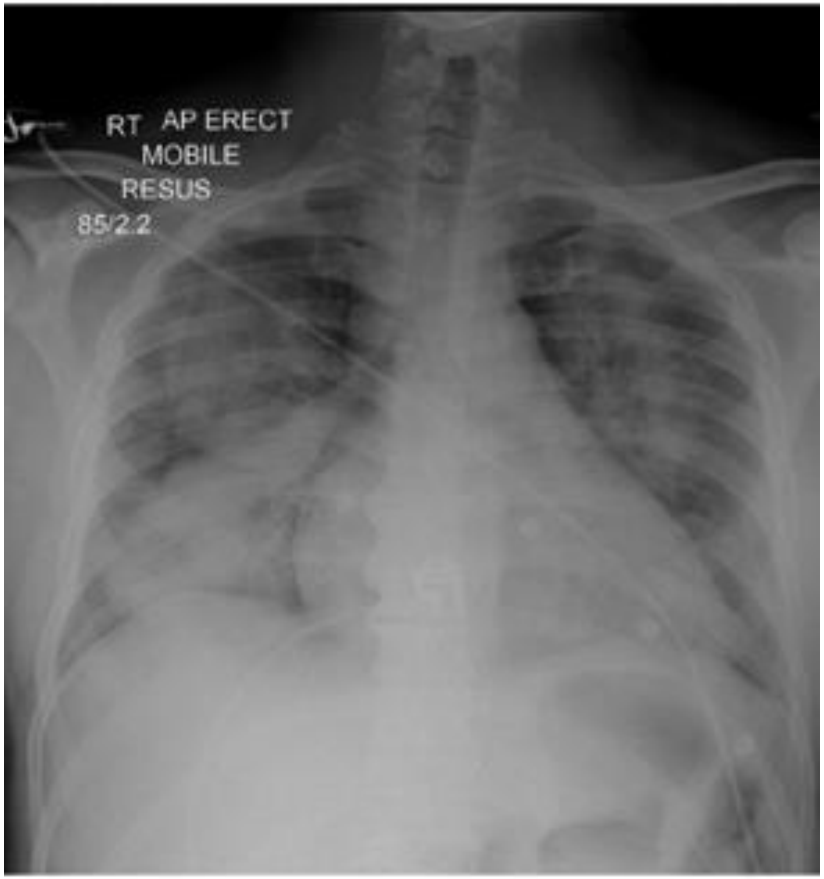
Dry cough

Low grade fever

Admitted from clinic with saturations 88% RA -> 80% on exercise

In setting of recent treatment x2 for acute cellular rejection, and early CMV viraemia which resolved with treatment

Case 1



- **CXR**

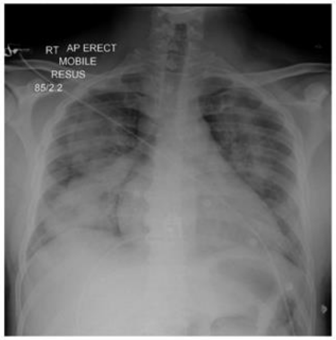
Bilateral predominantly perihilar consolidation

No significant pleural effusion

- **CT Thorax**

Multilobar consolidation and ground glass shadowing

Case 1



DDx (pulmonary infiltrates after transplant)

- **Infective**

***Bacteria*: Conventional bacteria, mycobacteria, nocardia**

***Viruses*: CMV, community respiratory viruses (influenza, parainfluenza, RSV)**

***Fungi*: Aspergillus, pneumocystis, cryptococcus**

- **Fluid**

***ARDS*: sepsis, drug reaction (campath, ATG)**

***Pulmonary oedema*: LV failure, diastolic dysfunction, transplant RAS (flash)**

Pulmonary haemorrhage

- **Medication**

***mTORi*: pneumonitis**

***Others*: azathioprine, cyclophosphamide, nitrofurantoin**

Case 1

- **Management:**

Broad spectrum antibiotics, empiric treatment dose co-trimoxazole, i/v gancyclovir

MMF held

Blood cultures sent

CMV level 2542 copies/ml

- **Rapid deterioration with respiratory failure**

-Intubated and ventilated ICU

-Bronchoscopy -> BAL specimens:

PCP stains negative

Case 1

- **Management:**

Broad spectrum antibiotics, empiric treatment dose co-trimoxazole, i/v gancyclovir

MMF held

Blood cultures sent

CMV level 2542 copies/ml

- **Rapid deterioration with respiratory failure**

-Intubated and ventilated ICU

-Bronchoscopy -> BAL specimens:

PCP stains negative

CMV inclusions visualised and PCR for CMV positive

Dx: CMV Pneumonitis

Case 1

- **Management**

Completed 2 weeks i/v gancyclovir (and other antibiotics)

CMV viraemia cleared

Quick clinical response

- **Progress**

Recovery from above

Last seen Sept 2017: creatinine stable around 200

CMV after transplantation

- **Herpesvirus (HHV-5)**
- **Commonest OI post-transplant: 40-50% recipients develop viraemia**
- **Primary infection in immunocompetent asymptomatic or mononucleosis-like illness**
- **Followed by latency – can reactivate e.g. i/s**
- **Transplant recipients can have**

Primary infection (D+/R-)

Reinfection (different strain) (D+/R+)

Reactivation (R+)

CMV after transplantation

- Viraemia strongly associated with donor and recipient CMV characteristics:

Risk viraemia: D+/R- > D+/R+ > D-/R+

- Other risk factors

Depleting antibody induction

Acute rejection

Poor graft function

Older donor age

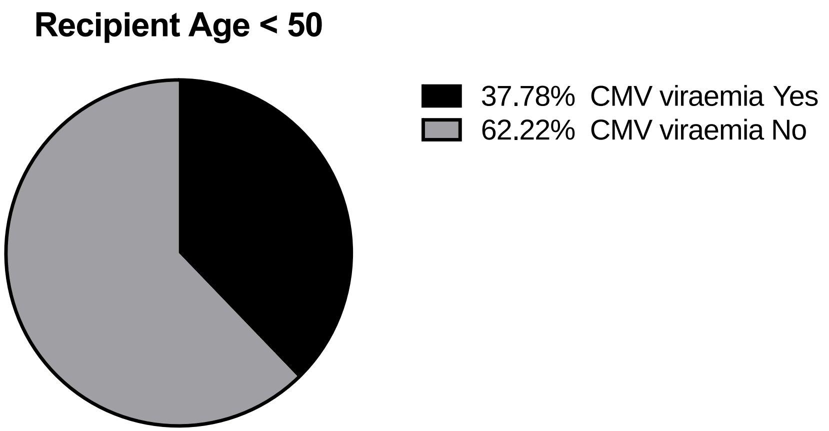
?older recipient age

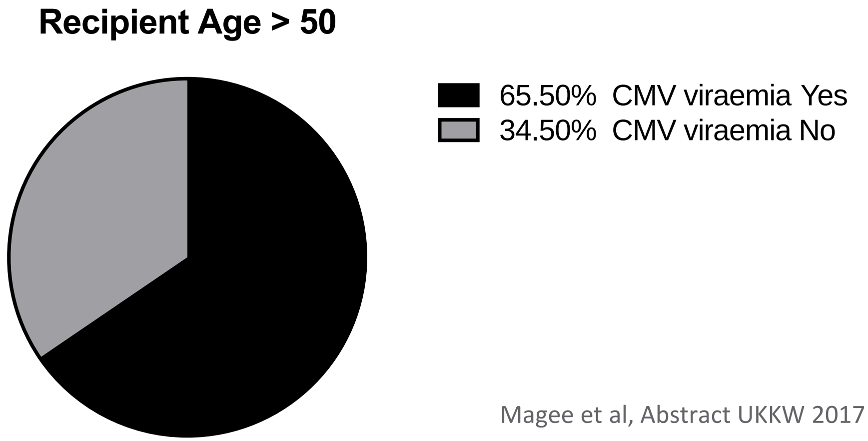
- Clinically

Most viraemic patients asymptomatic

Symptomatic disease in about 8% recipients

Correlation of VL with symptoms (but severe disease can occur with only low level viraemia)





Magee et al, Abstract UKKW 2017

CMV after transplantation

Table 4.Clinical characteristics of CMV infection post-transplant

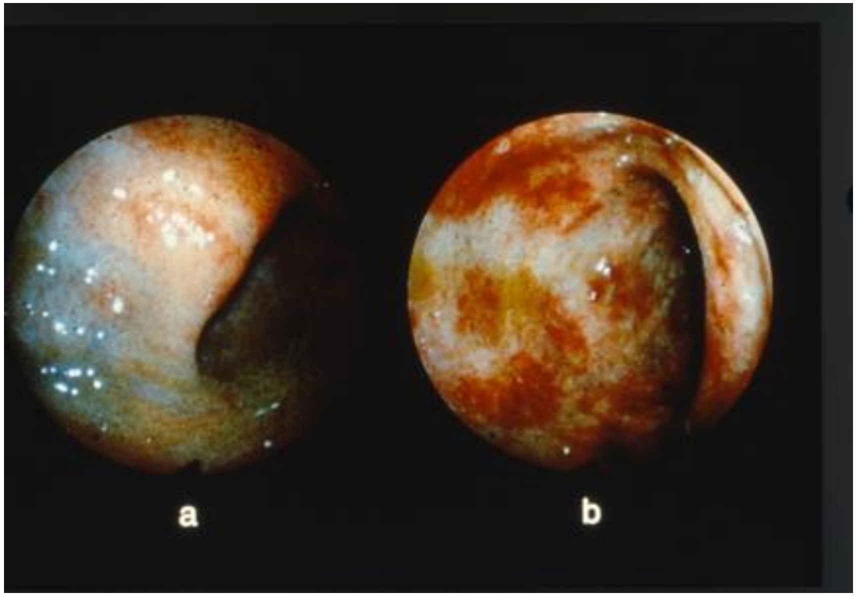
CMV viraemia	Often asymptomatic. Commonly associated with leucopenia or myelosuppression before developing CMV syndrome.
CMV Syndrome	Temperature >38°C for at least 2 days in the absence of another cause, plus CMV DNA viraemia and either neutropenia, thrombocytopenia, lymphocytosis, myalgia, headache or arthralgia.
Pneumonitis*	Interstitial pneumonitis with early desaturation. Can be rapidly progressive and may have co-infections such as PJP.
Upper GI	Gastritis/Duodenitis common symptoms in early primary infection, mouth ulcers and oesphagitis.
Lower GI*	Colitis - often bloody and may be fulminant.
Hepatitis	Raised transaminases and flu-like illness
Pancreatitis	Asymptomatic with raised amylase to fulminant pancreatitis
Encephalitis/Meningitis	Usually late feature
Retinitis	Usually a late manifestation in profoundly immunocompromised patients
Myocarditis	Usually late
Nephritis	Relatively rare but can result in graft failure or native kidney loss. May have characteristic 'owl's eye' appearance in biopsy
Cystitis	Relatively rare following SOT but can occur post-BMT

NB peripheral blood is usually, but not always, positive for CMV DNA in the presence of end-organ disease

CMV after transplantation

CMV retinitis (early)

CMV colitis (abdo pain and bloody diarrhoea)



CMV after transplantation

- **Most common 4-12 weeks post transplant**
- **Also**

Following treatment rejection

Cessation of prophylaxis

In D-/R- after primary infection (any time)

- **Diagnosis**

CMV PCR of blood and other appropriate specimen (BAL fluid, CSF)

CMV viral inclusions on biopsy specimen

CMV after transplantation

Prophylaxis (universal)

- All except D-/R- (low risk)
- Valgancyclovir (dose adjusted to renal function) for 6 months
- Monitor for late onset disease (after stopping treatment)
- Leucopaenia = common SE
- Resistance = concern

Pre-emptive therapy

- No prophylaxis
- CMV PCR twice weekly in clinic in first 3 months and after CMV treatment
- Rescue pack and treatment if CMV > 3000 copies/ml
- Dependent on robust monitoring and good communication with virology

RFH:
CMV viraemia 63% (D+/R-); 22% (D+/R+); 18% (D-/R+)
4.9% CMV syndrome
1% end organ disease

CMV after transplantation

- **Management**

CMV viraemia < 3000 copies/ml: I/S reduction
CMV viraemia > 3000 copies/ml: treatment
End organ disease (any CMV level): treatment

Treatment:
Oral valgancyclovir (treatment dose) or i/v gancyclovir (more severe disease)
Continue for 2 weeks minimum (RFH: until x 2 negative CMV PCR)
I/S reduction, if no rejection

Resistant CMV: cidofovir and foscarnet (nephrotoxic).

Relapse is common (esp D+/R-)

Possible anti-CMV effect with mTORi.
RFH (persistent/resistant CMV) if no further i/s reduction possible
Swap tacrolimus to sirolimus
Add sirolimus to lower dose tacrolimus (if increased rejection risk)

Case 2

- **46 year old female, white British, born and brought up in London**
- **T1DM since aged 10**

-retinopathy, neuropathy, and nephropathy

- **Pre-emptive SPK Transplant 2011**

-1,1,0 MM

-Alemtuzumab (*Campath*) induction, rapid steroid wean, Tacrolimus, MMF 1.5g/day

-CMV pos -> neg

-Co-trimoxazole and valgancyclovir prophylaxis (6 months)

Case 2

- Creatinine to 90-100, pancreas function, and well first 4 months

- 5 months post transplant:
- E.Coli (ESBL) transplant pyelonephritis -> ertapenem, then fosfamycin
- CMV viraemia (peak 9466 copies/ml) -> treatment dose valgancyclovir
- MMF held (2/52), reintroduced 1g/day, tac (levels 5-8)
- Creatinine blip to 150 but settled to baseline
- CMV cleared

Case 2

- **Next 12 months:**

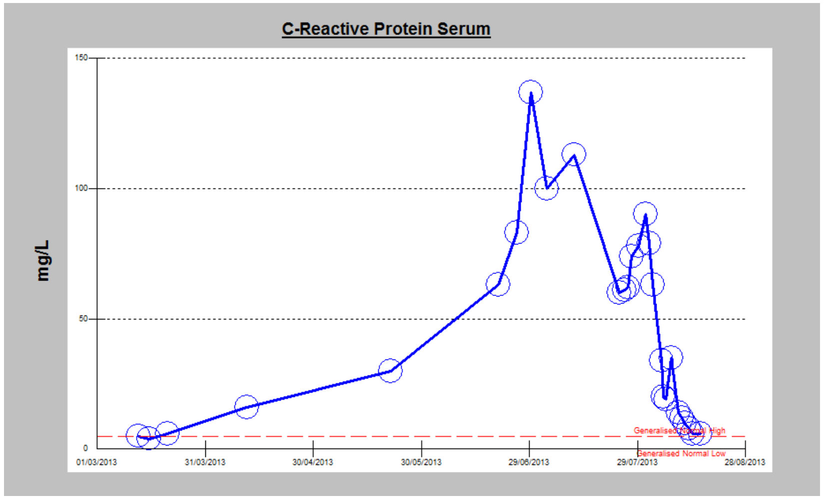
-x4 UTI (multiple organisms, most related to sexual activity). Normal urodynamics. Peri-coital antibiotics.

-stable graft function

- **18 months post transplant:**

-genital herpes: oral acyclovir

3-4 week history of painful dysphagia, retrosternal burning, and 3kg weight loss



Case 2

- Working diagnosis: infectious oesophagitis

-Candida
-HSV
-CMV (serum VL undetectable)

- OGD: severe oesophagitis, no candida, biopsy: negative CMV and HSV

- PPI (high dose), treated (empirically) for H. Pylori (amoxicillin and metronidazole)

- Persistent GI symptoms and worsening systemic upset

-fevers, further weight loss
-CRP >100 unexplained
-painful dysphagia
-some diarrhoea

- CT (chest, abdomen, pelvis): unremarkable

- MMF switched to azathioprine

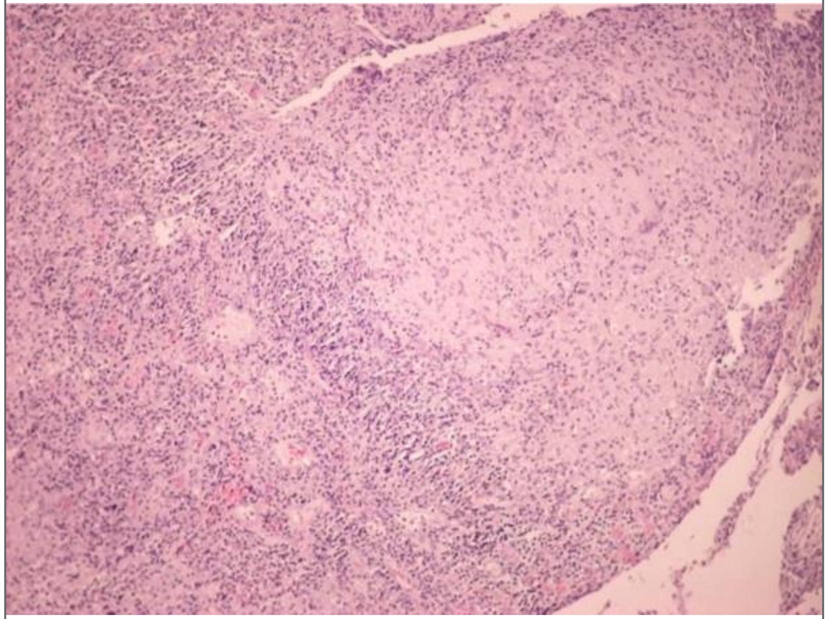
Case 2

- **Repeat OGD:**

-severe oesophagitis

-oesophageal stricture

Biopsy:



Case 2

- **Repeat OGD:**

-severe oesophagitis

-oesophageal stricture

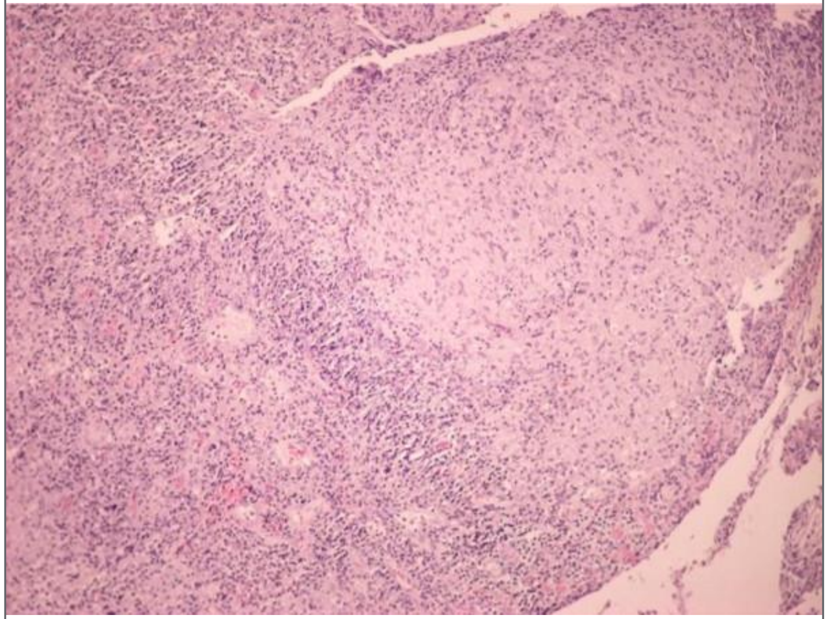
Biopsy:

-Necrotizing granulomatous inflammation

-ZN positive for AFBs

-TB PCR positive

- **Dx: TB Oesophagitis**



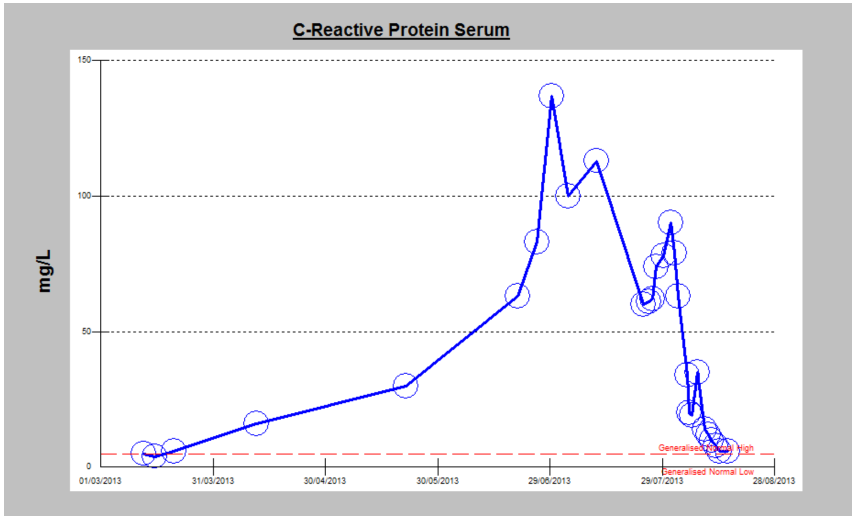
Case 2

- **Management**

-Quadruple anti-TB therapy (rifampicin, isoniazid, pyrazinamide, ethambutol) 6 months
-Tacrolimus dose increased
-NG feeding
-Serial oesophageal dilatations

- **Progress**

-renal function stable (creatinine 80-90)
-mild derangement in liver function on TB therapy
-constitutional symptoms settled
-weight gain and improvement oral intake
-maintained tacrolimus levels 5-8, azathioprine 50mg od



…..last seen in clinic Sept 2017: creatinine 101, just climbed mountain to celebrate 6th anniversary of transplant

TB after Transplantation

- **Incidence of active TB in renal transplants:**

-0.3-1% in US
-0.7-5% in Europe
-5-15% in India and Pakistan
(x20-70 general population)

- **Risk factors**

-country of origin
-diabetes
-chronic liver disease
-burden of i/s (inc.use of depleting antibodies)

- **Screening pre transplant challenging**

-Mantoux and IFNg release assays often result in false negatives in ESRD
-can get false positives post BCG, don't reliably distinguish latent and active disease

TB after transplantation

- **Prophylaxis**

-KDIGO: “we suggest that TB prophylaxis and treatment regimens be the same in KTRs as would be used in the local, general population who require therapy (2D)”

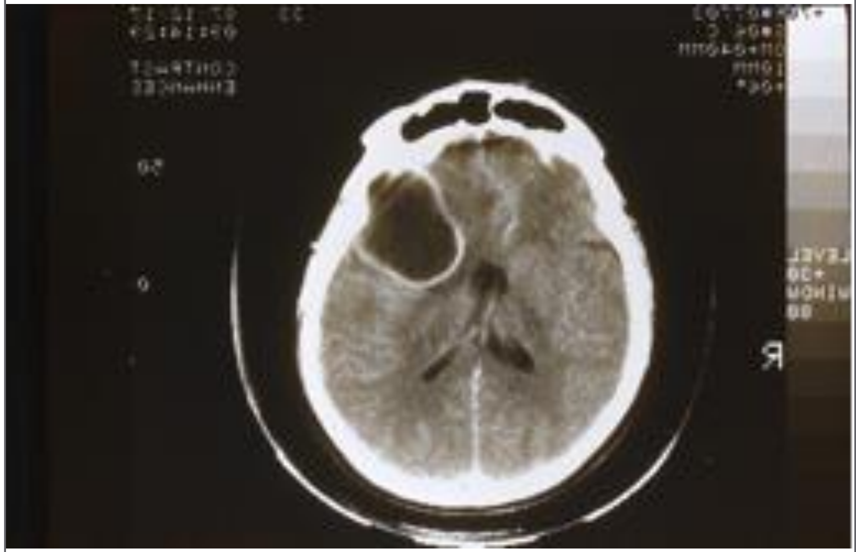
-local practice (London) prophylaxis with isoniazid 300mg/pyridoxine 25mg if:

History of TB not adequately treated
CXR findings consistent with previous TB, not adequately treated
Close contact with TB (family member/sharing accommodation)
Immigrated to UK within last 5 years from a highly endemic country (prevalence >40/100000 population)
[or transplanted in highly endemic country]
Donor from highly endemic country

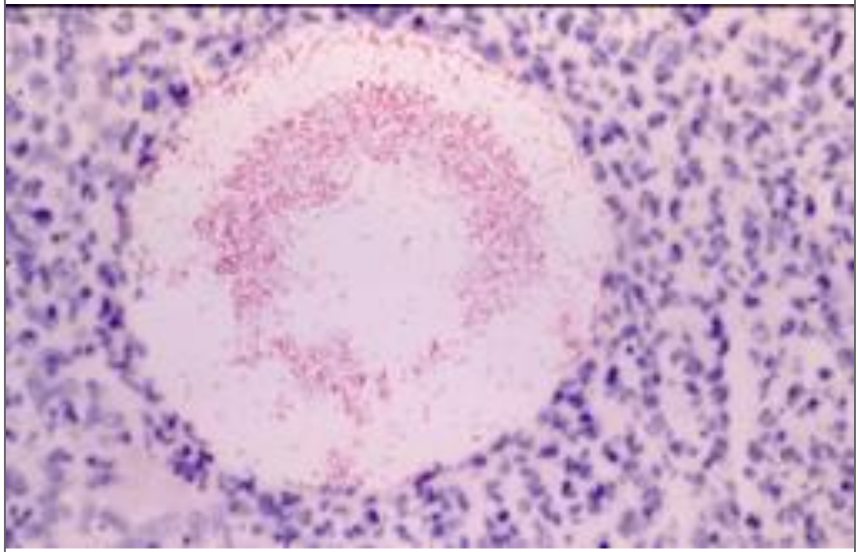
- **Presentation at average of 10-12 months**
- **Majority reactivation; 10% primary infection (donor derived infection rare)**
- **Fever (70%) and systemic upset (weight loss/asthenia) predominant symptoms**
- **Unexplained CRP**
- **<u>2/3rds present with extrapulmonary disease</u> (vs. 15% in general population)**
- **Ensuring tissue biopsy, ZN stain, and culture important in making diagnosis**

TB after transplantation

Frontotemporal tuberculoma (erratic behaviour)



Multiple AFB on skin biopsy (rash)



TB after transplantation

Lumbar vertebral destruction (back pain)

Wrist and finger joint swelling (atypical mycobacterial infection)

TB after transplantation

- **Management**

-standard anti-TB therapy

-NB. Rifampicin induction of cyt P450, therefore increase CNI up to x3 in first 2 weeks of therapy (reverse when stopping tx)

-often accompanied by reduction in i/s

-caution if TB in neurological site as can precipitate IRIS and lead to clinical deterioration

- **Reasonable outcomes (Canet *et al*, NDT, 2011)**

-hospital mortality 6%

-1 year graft survival 97%

Case 3

- 68 year old male, white British, born and brought up UK
- HIV

Diagnosed 1986, Antiretroviral therapy 2003

Undetectable VL, CD4 > 500

- Multisystem illness (2005) affecting kidney, parotid, eye and joints with granulomatous inflammation on renal biopsy -> sarcoid
- Progressive proteinuric CKD (sarcoid)

-2016 nearing ESRD

-switched to non protease inhibitor regimen (Abacavir/lamivudine/rilpivirune) with view to transplantation

Case 3

- **Live related pre-emptive kidney transplant from sister (June 2016)**

-0,1,1 MM

-CMV pos -> pos; HSV pos -> pos

-Basiliximab induction, methylprednisolone 40mg x3 -> prednisolone 20mg, Tacrolimus (standard dose), MMF 2g/day

-co-trimoxazole prophylaxis

-routine surgery and discharged day 7

-creatinine fallen to 146

Case 3

- **First transplant visit: intolerable GI symptoms –> reflux, nausea, vomiting, unable to eat**

-MMF switched to azathioprine 50mg od, prednisolone enteric formulation, aspirin held, ranitidine

- **Following week, GI symptoms settled, creatinine rise 146 -> 174, tac 10.4ng/ml**

-transplant biopsy (week 2): patchy T cell infiltrate, some acute tubular damage

-tx: methylprednisolone 500mg x3 pulse iv then prednisolone 20mg; azathioprine increase 50->100mg od

-creatinine 145-160

Case 3

- **Week 5: creatinine rise to 241 post stent removal**

-USS: dilated renal pelvis -> nephrostomy

-subsequent decompressed system on USS, no stent placed

-creatinine remained 240-250

-tac levels 10-12ng/ml

-CMV 4213 copies/ml -> valgancyclovir with good response

-serum BK and EBV undetectable

- **Week 6: further biopsy**

-heavy inflammatory cell infiltrate (no evidence BK) -> further methylprednisolone 500mg x3, azathioprine switched to myfortic 720mg bd

-creatinine to around 200

Case 3

- **Week 6 – 6 months**

-largely well in self

-creatinine around 200

- **6 months**

-readmission with rise in creatinine to 240

-USS hydronephrosis: nephrostomy, distal ureteric stricture on nephrostogram, stent

-creatinine back to 200

-subsequent ureteric reimplantation

- **Month 8**

Skin lesions developed: lower limb, flank and face

Purple and raised, not itchy.

Case 3

Case 3

- Biopsy consistent with Kaposi's sarcoma
- CT PET: no evidence of visceral involvement

Management:

- Reduction in I/S: myfortic 360 -> 180mg bd, Tacrolimus (aiming levels 5-6), prednisolone 5mg/day
- With i/s reduction alone, regression of KS lesions
- S/b clinical oncologist and radiotherapy to outstanding lesions
- Surgeons unhappy for switch to sirolimus until ureteric stent removed 8/52 post reimplantation
- Post stent removal, no significant proteinuria, some ongoing KS lesions -> myfortic changed to sirolimus (aiming levels 8-9) (July 2017; month 12)

Progress:

- Complete response in KS lesions
- Discharged from oncology
- Tacrolimus (5-6), prednisolone 5mg, sirolimus (8-9)
- Creatinine 184

Kaposi's Sarcoma after transplantation

- **Clinical manifestation of HHV-8 primary infection, reactivation, or reinfection**

- **Geographical bias in seroprevalence HHV-8**

Mediterranean

E. Europe

Middle East

Sub-Sahara Africa

- **Prevalence x500 in solid organ transplant vs. general population**

0.05% transplant recipients NW Europe

5% Saudi Arabia

Kaposi's Sarcoma after transplantation

Table 6 : Risk Factors for the Development of Kaposi's Sarcoma post-transplant

Serostatus of Donor/Recipient	Data suggesting both that reactivation and primary infection at transplant are significant risk factors.
Geographical location	Mediterranean, Middle East, Eastern Europe and Sub-Saharan Africa
Burden of Immunosuppression	Overall burden of immunosuppression important especially depleting mAb
Age of recipient	>50 years
Homosexual Males	Multiple partners
Transfusion	In high prevalence areas

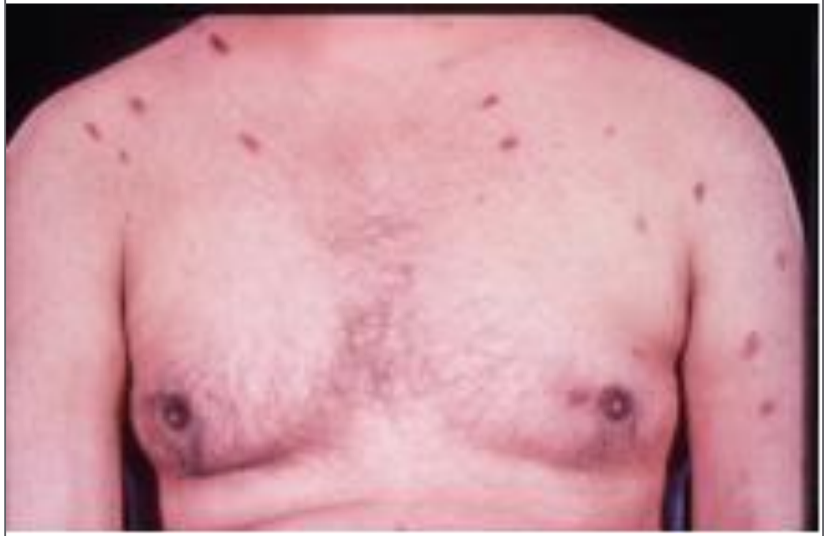
Kaposi's Sarcoma after transplantation

- **Clinical presentation – Cutaneous**

Red/purple/black nodules

Typically lower body +- oedema

Kaposi's Sarcoma after transplantation



Kaposi's Sarcoma after transplantation

- Clinical presentation – Visceral

Lymphadenopathy
Pulmonary nodules
Pleural effusions
GI disease –inc. Bleeding

- Diagnosis

Biopsy and histology
(any suspicious skin lesion; high index suspicion GI lesions)

- Management

Reduction i/s (complete cessation if life threatening visceral disease)

London:
-minimise/stop antiproliferative
-No response 2-4 weeks:
convert non-proteinuric patients from CNI to mTOR inhibitor (antiVEGF activity)
Alternative: mTORi and lower dose CNI (e.g previous rejection)

If can't use mTORi, stepwise small cuts in CNI

Radiotherapy to cutaneous lesions

Aggressive visceral disease: chemotherapy (bleomycin, adriamycin, taxols)

- Prognosis

Mortality with visceral involvement 10%
Graft loss common due to rejection post ISR

Can recur in subsequent transplants – London: avoid heavy induction, plan for early switch to mTORi if possible

Summary

- **Infection after transplant common cause graft deterioration, morbidity and mortality**
- **Due to i/s, infections may present without gross systemic upset and in atypical sites**
- **Consider an infective process in unexplained symptoms**
- **Investigate unexplained CRP**
- **Put 'infective presentations' in to the context of**

Timing post transplantation

Serological characteristics of donor and recipient

I/S burden

Antimicrobial prophylaxis used