Difficult to treat infections in renal transplant recipients—local experience

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Outline

- Cytomegaovirus infection (CMV) infection in renal transplant
- Pneumocystis Carinii/Jirovecii pnuemonia (PCP) in renal transplant
- Recurrent urinary tract infection (UTI) in renal transplant

CMV infection—case report

- Male/28 Mr. X
- Suspected reflux nephropathy since childhood with progressive renal failure
- On peritoneal dialysis since March 2002
- Cadaveric renal transplant 24 Feb 2003
- 3 mismatch
- Induction with Basiliximab (Simulect), Cyclosprin A, Azathiorpine and Corticosteroid
- Immediate graft function
- Recipient anti-CMV IgG –ve
- Donor anti-CMV IgG +ve
- Oral Acyclovir as anti-viral prophylaxis

CMV infection—case report

- Developed fever and found CMV pp65 +ve
- Started IV ganciclovir 125mg Q12H for 14 days with clinical response
- Change back to oral acyclovir prophylaxis and disease recurred again
- CMV pp65 level increased to 230 per 2x10^5 WBC
- 2nd course of IV ganciclovir with double dose 250mg Q12H for 21 days
- CMV pp65 level decreased to negative
- Switched to oral acyclovir prophylaxis again

CMV infection—case report

- Serial monitoring of CMV pp65 showed increase in level again, up to 410
- 3rd course double dose of IV ganciclovir given for 39 days (stopped 2 weeks after negative CMV pp65 level)
- Switched to oral ganciclovir 1gm tds prophylaxis
- Recurrence of CMV disease again. Despite 4 weeks of double dose IV ganciclovir, CMV pp65 level climbed up to 622

CMV infection—case report

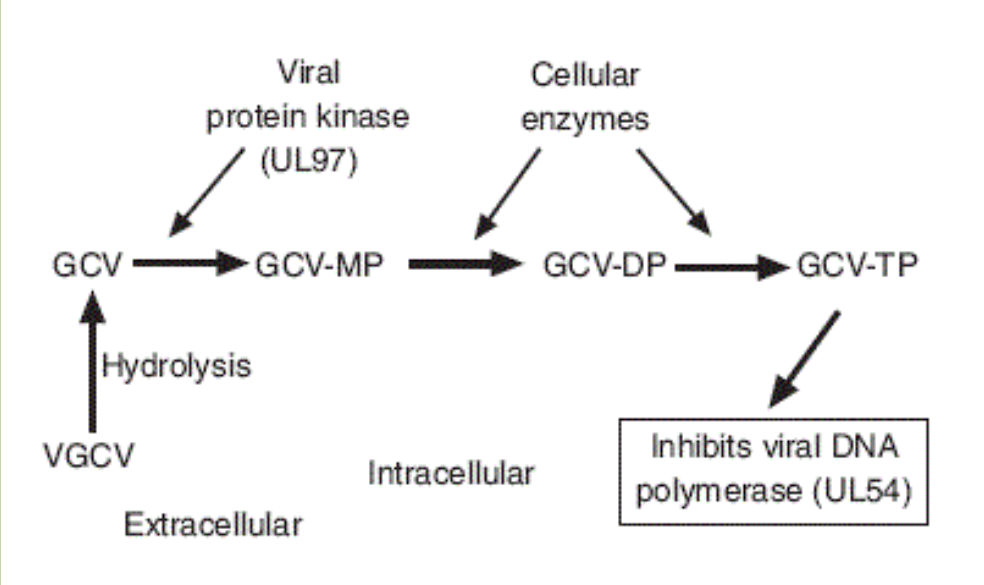
- Foscarnet 2gram Q12H was added with CMV pp65 level dropped negative 3 weeks after the combination treatment
- Foscarnet was continued for 1 week more while IV ganciclovir was continued 1 month more after the negativity of CMV pp65
- Azathioprine was reduced at 6 months post transplant (100mg daily to 50mg daily), and eventfully discontinued at 9 months post transplant
- Cyclosporin A level was kept low after 10 months post transplant
- No more recurrence after stopped all anti-viral treatment at 9 months post transplant and no more prophylaxis was given

CMV infection—case report

- Summary
  - Recurrent CMV disease
  - Oral Acyclovir and ganciclovir failed to prevent disease recurrence
  - Highly suspected ganciclovir resistance which was successfully treated with add on Foscarnet
  - Azathoprine stopped and Cyclosporin A was kept at low level at around 9 months post transplant
  - No more recurrence after 9 months post transplant

Resistant CMV infection

- Cause of ganciclovir resistance
  - Ganciclovir is a guanosine analogue that inhibits CMV DNA polymerase
  - Phosphorylated in three steps to a triphosphorylated active form



Resistant CMV infection

- Cause of ganciclovir resistance
  - Mutations arising in UL97 phosphotransferase
  - Mutations arising in UL54 DNA polymerase
  - UL97 mutations are heterogenous conferring different degrees of ganciclovir resistance.
  - UL97 mutations accounts for 90% of resistant cases
  - Prolonged exposure to ganciclovir can give rise to simultaneous UL54 and UL97 mutations.
  - UL54 mutations can confer cross-resistance to foscarnet and cidofovir since these agents also target on CMV DNA polymerase

Chou S et al. *J Infect Dis 2002:185:162-9.*
Limaye AP. *Clin Infect Dis 2002;35:866-72.*
Jabs DA et al. *Am J Ophthalmol 2003;135:26-34.*

Resistant CMV infection

- Detection of resistance
  - Phenotypic assay
    - Viral culture with different concentration of ganciclovir to determine the concentration to inhibit 50% of CMV growth
    - Clumsy and time consuming. Long turnaround time leads to impractical clinical use
  - Genotypic assay
    - Assess for known mutations in the UL54 and UL97 genes
    - Not widely available
  - Clinical suspicion
    - No improvement (or with relapses) in CMV viremia or clinical disease during prolonged antiviral therapy especially in the presence of risk factors

Kotton CN at al. Transplantation 2013;96: 333-360

Resistant CMV infection

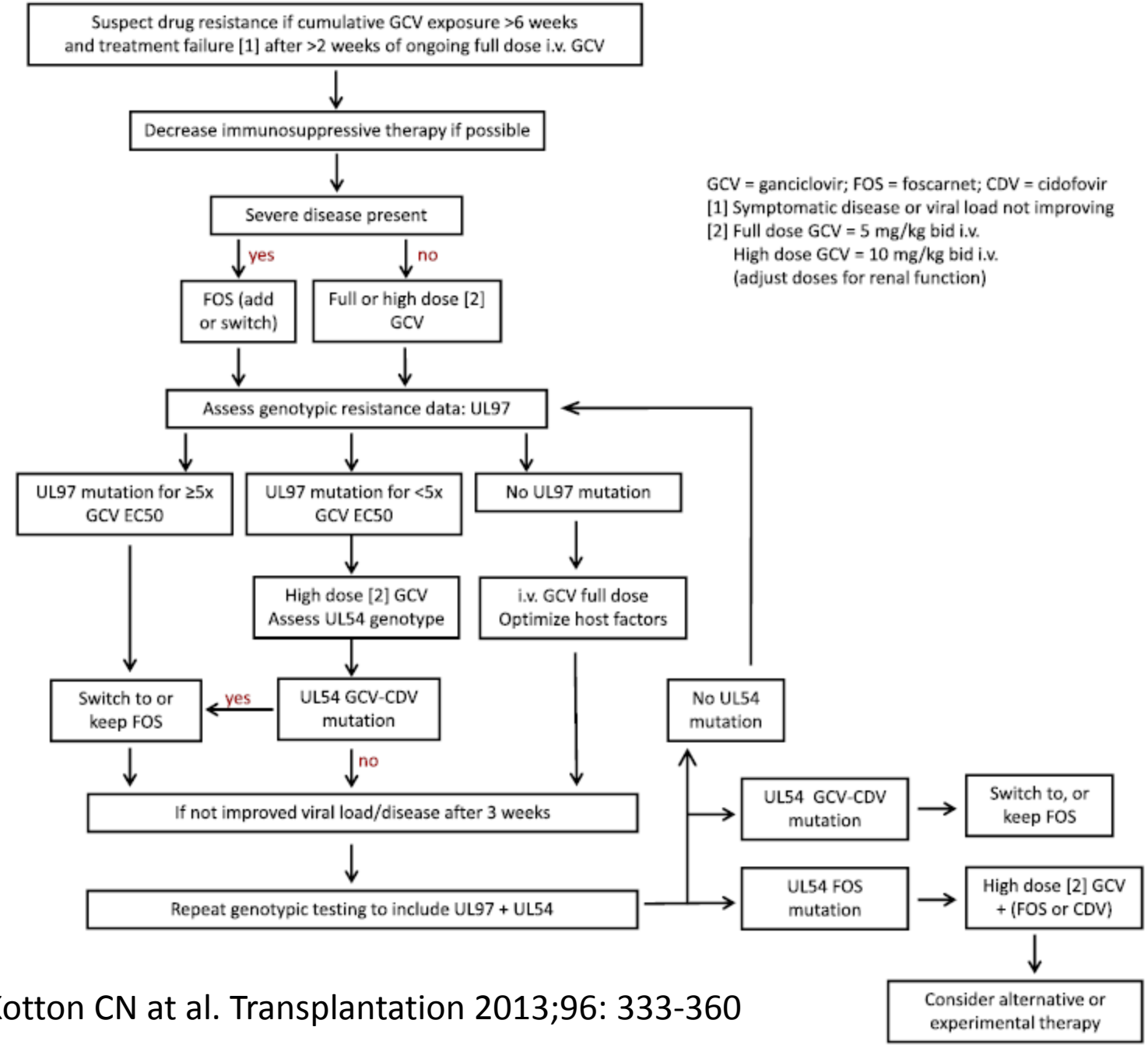
- Risk factors of resistance
  - Prolonged antiviral drug exposure esp. intravenous ganciclovir
  - Ongoing active viral replication
    - *Lack of prior CMV immunity i.e. D+/R- subset, with resistance ranged from 5-12% after viraemia*
    - High levels of immunosuppressive therapy
    - Inadequate antiviral drug delivery
  - The duration and the use of CMV prophylaxis appear not affecting the emergence of resistance

Lurain NS at al. Clin Microbiol Rev 2010; 23: 689.

Resistant CMV infection

- Treatment strategy
  - UL97 mutations appears first, followed by UL54 mutations
  - UL97 mutations are variable, therefore increasing the dose of ganciclovir to high dose may be effective
  - In severe cases, switch to, or add on Foscarnet should be considered since the UL54 mutations could possibly present which leads to increased ganciclovir resistance

Kotton CN. *American Journal of Transplantation 2013; 13: 24–40*



Kotton CN at al. Transplantation 2013;96: 333-360

Resistant CMV infection

- Newer agents
  - CMX001
    - Converted intracellularly to cidofovir
    - Not concentrated in the renal tubules like cidofovir and is thus less likely to have nephrotoxicity.
    - 400 times more potent than cidofovir against CMV
    - Limited marrow toxicity
  - The terminase inhibitor AIC246 (Letermovir)
    - Excellent anti-HCMV activity *in vitro and in vivo*
    - Has been successfully used to treat resistant CMV.

Marty FM et al. N Engl J Med 2013 Sep 26; 369:122

Kaul DR et al. Am J Transplant 2011; 11: 1079–1084.

Resistant CMV infection

- Artesunate
  - Antimalarial
  - Anti-CMV effects that may be helpful in resistant case
  - Case report showed effective in mild resistance cases but not in severe cases
- Leflunomide
  - Has antiviral activity to clear CMV viremia with resistant CMV
  - Case report showed clearing up of CMV viremia when replacing mycophenolate mofetil, despite resistance to double dose IV ganciclovir

R. Germi et al. Antiviral Research, 2014(101), 57–61

Ciszek M. et al. Ann Transplant, 2014; 19: 60-63

Resistant CMV infection

- Debate
  - Reduction in immunosuppressions should be considered, but how much should immunosuppressants be reduced after CMV infection?
    - Stopping antimetabolite?
    - Reducing CNI and antimetabolite?
    - Switching to less potent immunosuppressants?
  - The presence of CMV infection has been associated with the development of rejection
    - Resuming higher dose of immunosuppressants after treatment success?

PCP infection—case report

- M/43 Mr. Y
- Diabetes with retinopathy and nephropathy
- HT
- Cadaveric renal transplant in HK 8 years ago
- 5 mismatch
- Donor and recipient CMV IgG +ve
- Maintenance immunosuppressant: Cyslosporin A, azathioprine and corticosteroid
- Acute cellular rejection type IA 1 year after transplantation
- Azathorprine switch to MMF afterward

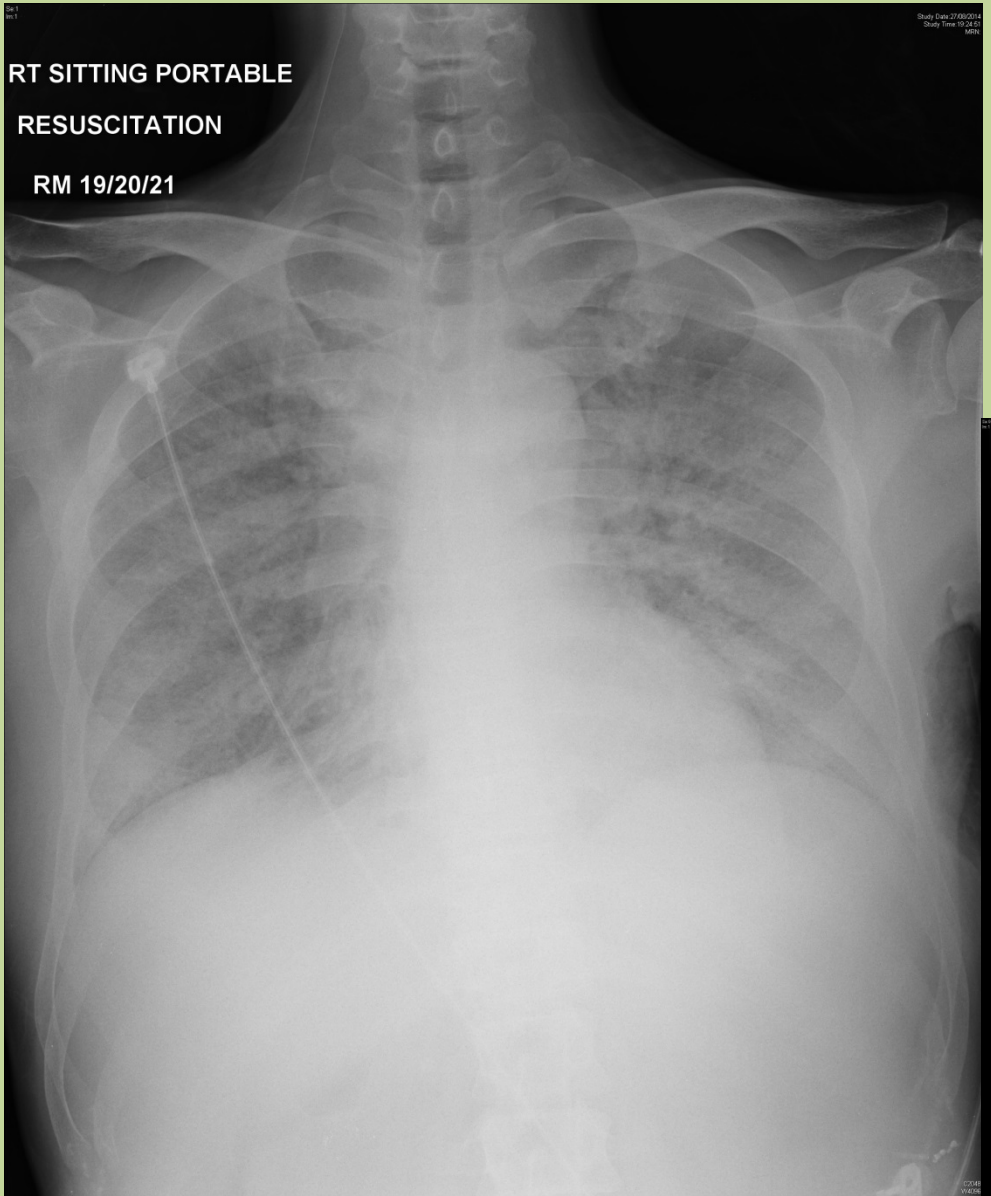
PCP infection—case report

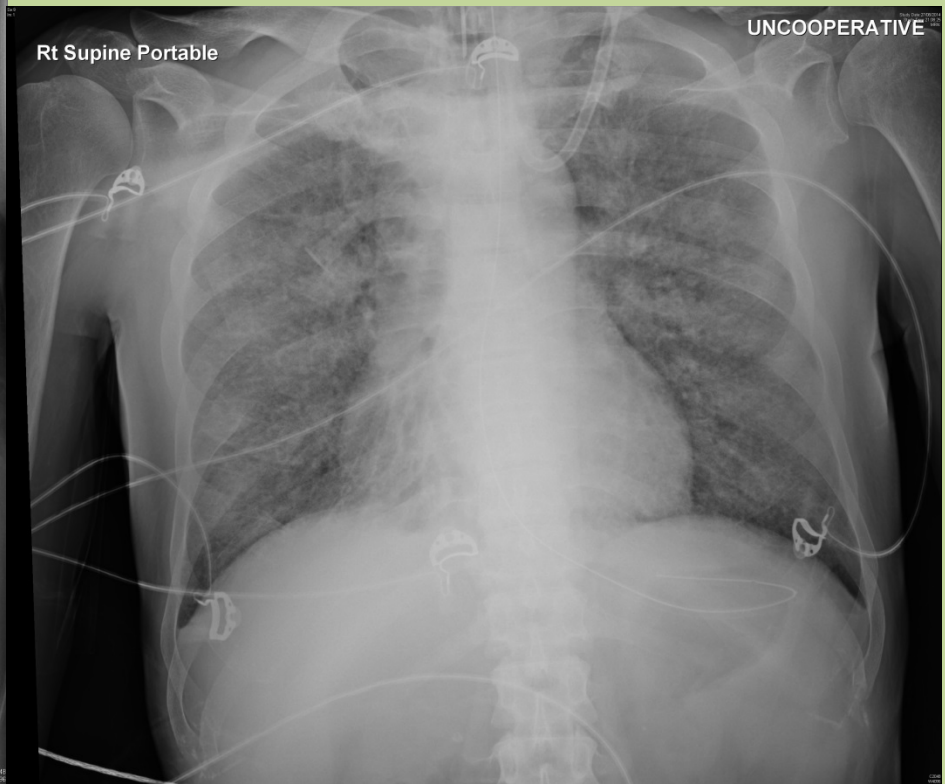
- Progressive renal failure for report biopsy
- Again cell mediated rejection Banff IA and significant glomerulosclerosis
- Pulse steroid + switched cyclosporin A to tacrolimus
- Tacrolimus level gradually titrated down from 14.7 ug/L to 4.7 ug/L
- No significant infection before this admission
- Creatinine level fluctuated from 350umol/L to 440umol/L

PCP infection—case report

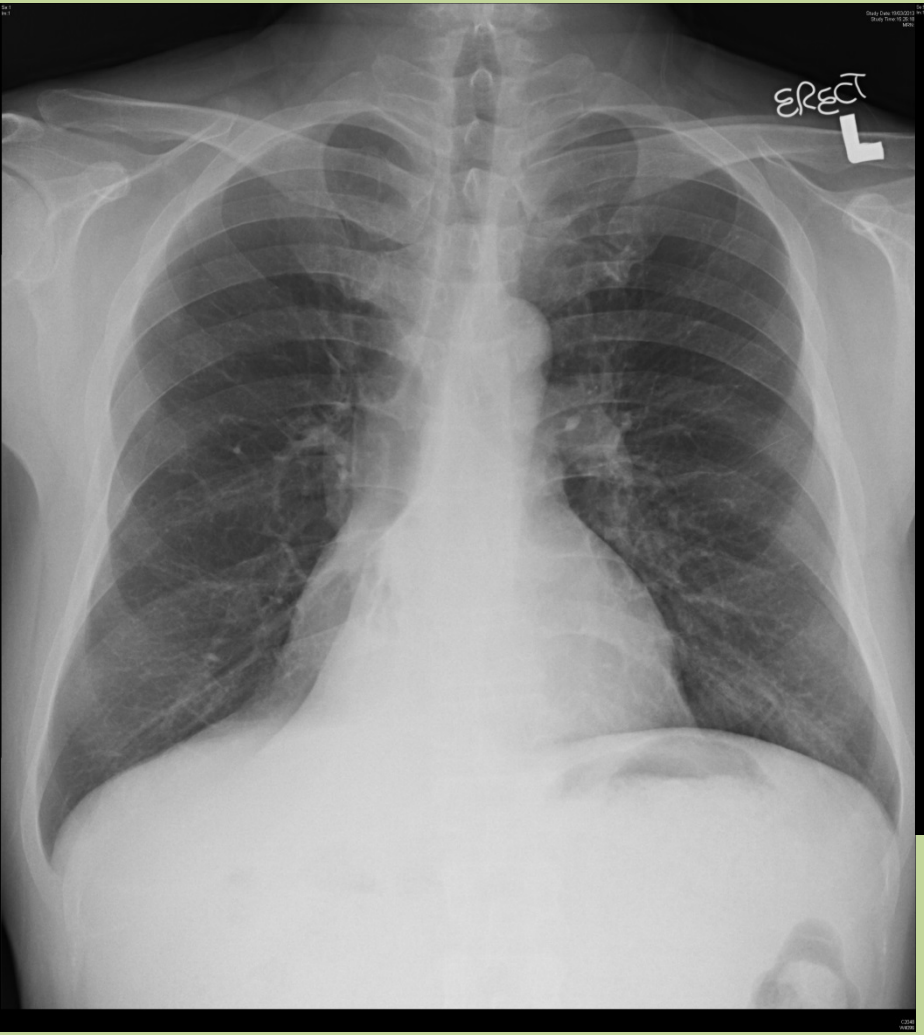
- Admitted for 1 week of shortness of breath, dry cough and loss of appetite
- Significant desaturation with SpO_2 85% on high flow O_2
- He required invasive ventilatory support in Emergency department
- Transferred to ICU

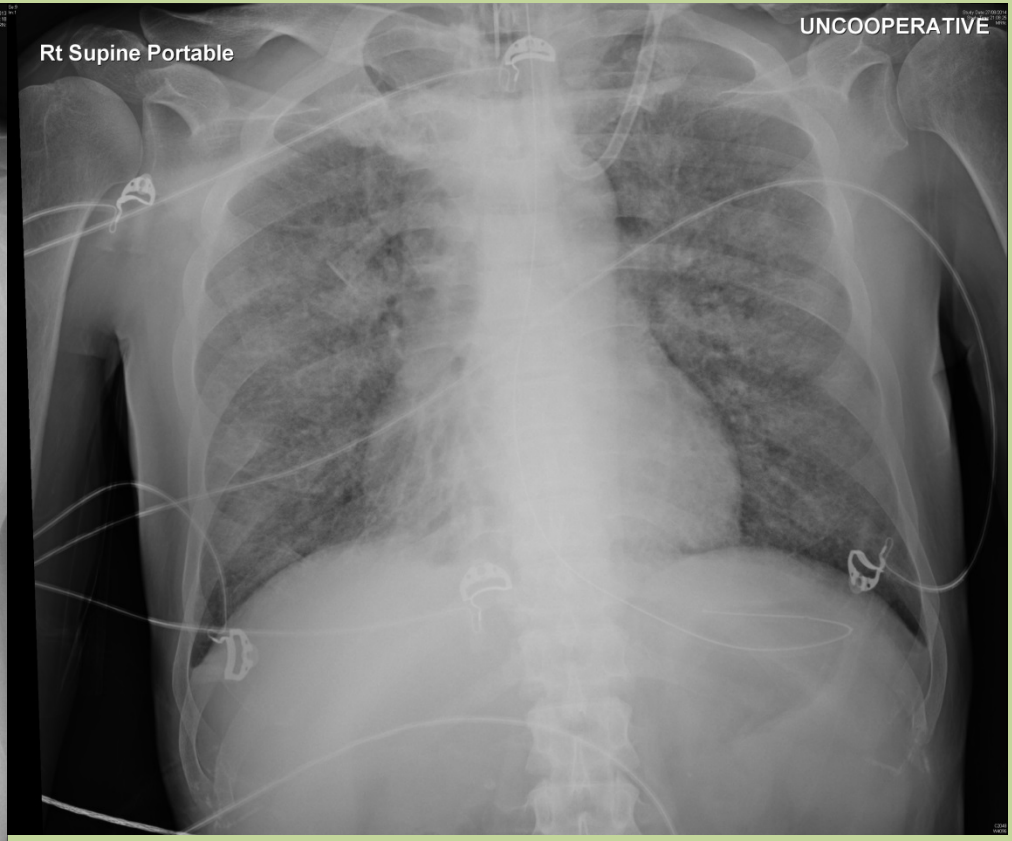
PCP infection—case report





PCP infection—case report

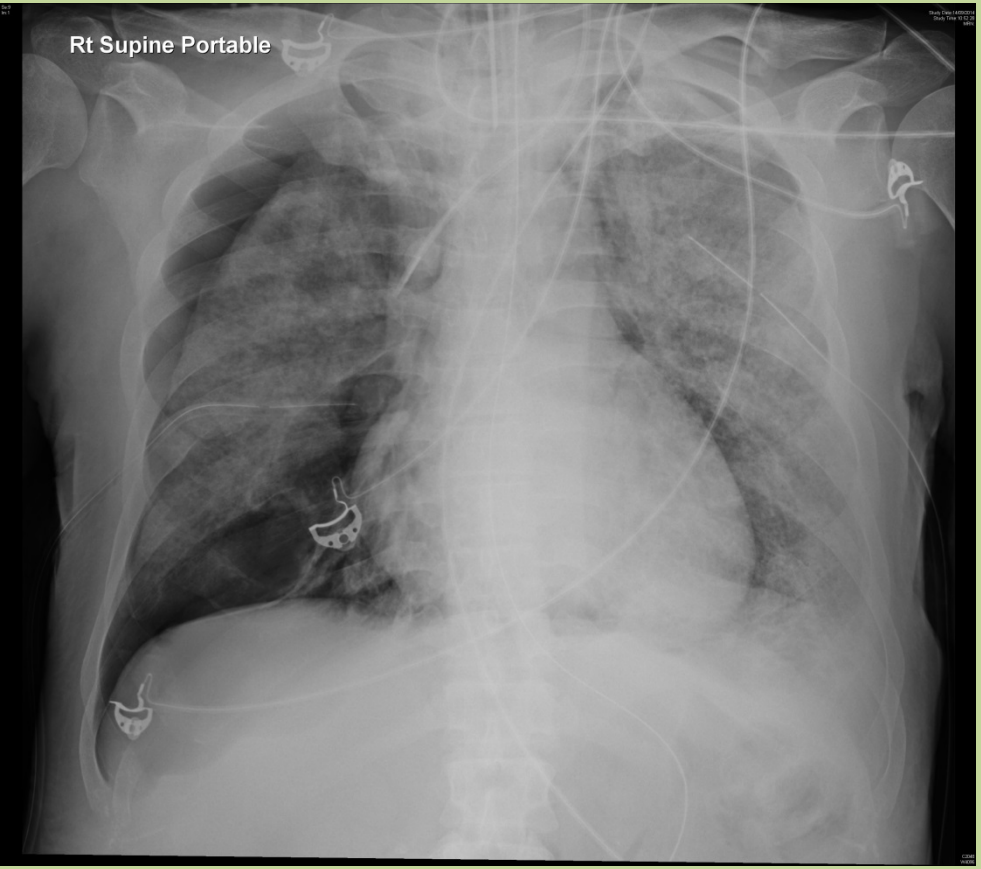




PCP infection—case report

- Empirical treatment with meropenem and doxycycline
- Started on Pentamidine 240mg Q12H the next day after admission
- Bronchoscopy and BAL saved on the day of admission, which confirmed presence of Pneumocystis carinii
- Extubated 3 days after admission
- Concurrently found CMV pp65 antigaemia positive (13/2x10^5 WBC)
- Started on renal dose IV ganciclovir

PCP infection—case report



- Noted SpO_2 desaturation again 9 days afterward required re-intubation
- Switched to IV clindamycin 600mg Q8H + oral primaquine 30mg daily
- Complicated with bilateral pneumothorax 2 days after re-intubation

PCP infection—case report

- Developed methaemoglobinaemia with level up to 14.1%, gradually improved after stopped primaquine
- Resumed IV pentamidine after stopped primaquine
- CMV pp65 antigaemia improved to 1/2x10^5 WBC after 2 weeks ganciclovir treatment
- Further complicated with candida albicans and imipenem resistant pseudomonas aeruginosa VAP, given anidulafungin, cirpofoxacin and gentamicin

PCP infection—case report

Gram Stain :-

Gram stain	Gram negative bacilli predominating
White blood cells :	Profuse
Epithelial cells :	Scanty

Culture :-

Organism 1 : Pseudomonas aeruginosa (Heavy growth (predominating))

ANTIBIOTICS	ORGANISM 1
Cefepime	R
Ceftazidime	R
Ciprofloxacin	S
Cotrimoxazole	R
Gentamicin	S
Imipenem	R
Levofloxacin	S
Meropenem	R
Piperacillin	R
Sulperazon	R
Timentin	R

S:SUSCEPTIBLE I:INTERMEDIATE R:RESISTANT
MR:MODERATE RESISTANT +:POSITIVE -:NEGATIVE

Comment :-

Serious Pseudomonas aeruginosa infection should be treated by combination therapy e.g. beta-lactam antibiotics plus aminoglycosides or quinolones.

PCP infection—case report

- All along put on intermittent haemofiltration support
- Progressive oliguria
- Passed away 1 month after admission

PCP

- Risk factors
  - Glucocorticoid use,
  - Defects in cell-mediated immunity,
  - Malignancy, particularly hematologic malignancies
  - Hematopoietic stem cell transplant (HSCT) or solid organ transplant recipients,
  - Rheumatologic diseases,
  - Severe combined immunodeficiency,
  - Severe malnutrition

Gilroy, SA et al. Seminars in Respiratory and Critical Care Medicine: 32(6), 2011, 775–782

PCP

- The risk is greatest in patients receiving the most intensive immunosuppressive regimens
- Certain chemotherapeutic drugs associated with increased risk are fludarabine, vincristine and cyclophosphamide.
- Without prophylaxis the risk could be as high as 5-15%

Gilroy, SA et al. Seminars in Respiratory and Critical Care Medicine: 32(6), 2011, 775–782

PCP

- Trimethoprim–Sulfamethoxazole (TMP-SMX)
  - The preferred treatment for PCP
  - Empirical treatment is recommended in suspected patients while cytopathology is not altered early in the treatment course
  - In severe case with PaO_2 <70 mm Hg, intravenous TMP-SMX is recommended
  - Mild to moderate PCP may be treated orally

Gilroy SA et al. Seminars in Respiratory and Critical Care Medicine: 32(6), 2011, 775–782

PCP

- Trimethoprim–Sulfamethoxazole (TMP-SMX)
  - Mechanism of toxicity
    - Trimethoprim is known to decrease the tubular secretion of creatinine, leading to mild elevations of the serum creatinine level
    - Trimethoprim decreases potassium excretion by alteration of the transepithelial voltage in the distal renal tubule
    - Acute intersitial nephritis could also be the possible cause
    - May form crystals in the urine of volume-depleted patients, resulting in AKI, and crystalluria may be seen in 0.4%–49% of these patients
    - AKI was reported to be very low in previous studies

Fraser TN. J Antimicrob Chemother 2012

PCP

- Trimethoprim–Sulfamethoxazole (TMP-SMX) *package insert*
  - Pharmacology: Primarily renal excretion
  - Contraindications:…. Is contraindicated in patients with marked hepatic damage or with severe renal insufficiency when renal function status cannot be monitored.
  - Renal dosing
    - CrCl > 30 ml/min — Usual standard dose
    - CrCl 15-30ml/min — Half standard dose
    - CrCl < 15ml/min — Use not recommended

PCP

- Trimethoprim–Sulfamethoxazole (TMP-SMX) dosing review
  - Measured or estimated creatinine clearance:
    - >30 ml/min - full dose
    - 15 to 30 ml/min - half dose (the concentration of active SMX may be reduced, relying on TMP activity only);
    - <15 ml/min - avoid drug if possible since the *SMX metabolites* will accumulate to potentially toxic concentrations unless dosage reduction in implemented, which would result in inadequate active SMX exposure.
  - HD: 7.5 mg/kg after each four hour HD session (initial 24 to 48 hours at 15 mg/kg/day).
  - CAPD: same as CrCl <15ml/min
  - CVVHD or Slow extended daily hemodialysis (SLED): 15 mg/kg/day TMP for Pneumocystis jovenii and equivalent infections; avoid underdosing with CVVHDF to avoid inadequate concentrations.

Glen R Brown. Annals of Intensive Care 2014, 4:13

PCP

- Pentamidine
  - Recommended for the treatment of severe PCP in patients allergic to or intolerant of sulfonamides.
  - 3 to 4 mg/kg intravenous daily for 21 days.
  - Significant side effects including ventricular arrhythmias, hyperkalemia, azotemia, hypoglycemia and hyperglycemia, leukopenia, thrombocytopenia, hypertension and hypotension, hepatic dysfunction, and pancreatitis

Gilroy, SA et al. Seminars in Respiratory and Critical Care Medicine: 32(6), 2011, 775–782

PCP

- Clindamycin–primaquine (C-P)
  - A cohort study of 57 patients: C–P (*n* = 23) or TMP-SMX (*n* = 34).
  - Non-significant higher failure rate on C-P (30.4 versus 20.6 %, *p* = 0.545)
  - The difference was more pronounced in severe PCP on C-P (60 versus 37.5 %,*p* = 0.611)
  - A significantly lower efficacy of C–P was seen when used as salvage therapy
  - Switching from C-P to TMP-SMX in C-P failure case were all successful, but not vice versa

Nickel P et al. Infection: December 2014, 42(6), 981-989

PCP

- Atovaquone
  - An alternative treatment for mild to moderate PCP in patients who are contraindicated to TMP-SMX
  - Recommended dosing: 750 mg orally twice daily before a meal for 21 days.
  - Adverse reactions: rash, fever, nausea, and abnormal liver function test.

Gilroy, SA et al. Seminars in Respiratory and Critical Care Medicine: 32(6), 2011, 775–782

PCP

- PCP and renal transplant recipient
  - Because of high mortality and morbidity, PCP prophylaxis should always be considered in high risk immunosuppressed patients
  - Reduction of immunosuppressants during the course of PCP should always be considered, esp. if poor response to treatment
  - Renal transplant recipient, when failed treatment of the acute rejection, often faced the unfavourable condition of both renal failure and escalated immunosuppressive state. Use of TMP-SMX should always be considered especially when failed other treatment, even when the renal failure approached end stage

Recurrent UTI—case report

- Female/65 Ms Z
- Unknown cause of ESRD on peritoneal dialysis
- Cadaveric renal transplant in China
- Details of the perioperative course unknown
- Maintained with cyclosoprin A, MMF and steroid
- ACUTE REJECTION (Banff's grade IB) treated with pulse steroid few months after transplant
- CMV infection treated successfully with IV ganciclovir

Recurrent UTI—case report

- Developed recurrent urinary tract infection with different gram –ve organism including ESBL producing E. coli, klebisella, pseudomonas and citrobacter. Repeated treatment with broad spectrum antibiotics (4 episodes in 6 months)

Recurrent UTI—case report

- Ix of recurrent UTI
- Micturation cystourography:
- FINDINGS:
  - Urinary bladder outline is smooth.
  - Reflux of contrast up to the calyceal system of the transplant kidney.
  - There is mild dilatation of the calyceal system.
  - The ureter is not dilated.
- IMPRESSION:
  - Grade III-IV vesicoureteric reflux to the transplant kidney.

Recurrent UTI—case report

- Re-implantation of ureter performed
  - Transplanted ureter dissected away from bladder
  - Boari flap harvested
  - Ureter spatulated & reimplanted into the flap with submucosal tunnel
- MCU 4 months afterward
  - There is reflux of contrast up to the level of the mid ureter of the transplanted kidney in the left lower quadrant of the abdomen. No The reflux of contrast into the native urinary system seen
- Comment:
  - Vesicoureteric reflux into the transplanted urinary system is still observed, however, the extent is significantly reduced.

Recurrent UTI—case report

- Episodes of UTI was reduced to 4 times over 6 years
- MMF changed to Azathioprine 1.5 year after the reimplantation due to financial reason

Recurrent UTI

- Risk factors
  - Female gender
  - History of an acute rejection episode and/or a cytomegalovirus (CMV) infection.
  - All patients with vesicoureteral reflux of strictures at the ureterovesical junction suffered recurrent UTIs (*n=7).*

Golebiewska J. et al. Transplantation Proceedings; 2011(43), 2985–2990

Table 2. Comparison of Risk Factors Between UTI Patients and Non-UTI Patients

	Non-UTI (n = 50)	All UTI (n = 50)	*P*
PCKD	2 (4.0%)	2 (4.0%)	1.000
BPH	0/13 (0.0%)	2/11 (18.2%)	.480
CMV infection history	1 (2.0%)	3 (6.0%)	.617
Retransplantation	1 (2.0%)	1 (2.0%)	1.000
Complex renal cyst	6 (12.0%)	9 (18.0%)	.401
Renal calculi	4 (8.0%)	12 (24.0%)	.029
D-J cath insertion	7 (14.0%)	10 (20.0%)	.424
Ureteral stricture	3 (6.0%)	7 (14.0%)	.182
Technical complications with ureteral anastomosis	3 (6.0%)	4 (8.0%)	1.000
VUR	1 (2.0%)	5 (10.0%)	.204
DM	8 (16.0%)	23 (46.0%)	.001

Abbreviations: PCKD, polycystic kidney disease; D-J cath, double J ureteral catheter.

Lim JH et al. *Transplantation Proceedings, 2013:45, 1584–1589*

Table 4. Comparisons of Risk Factors Between Recurrent and Nonrecurrent UTI Patients

	Nonrecurrent UTI (n = 27)	Recurrent UTI (n = 23)	*P*
PCKD	1 (3.7%)	1 (4.3%)	1.000
BPH	0/8 (0.0%)	2/6 (33.3%)	.165
CMV infection history	0 (0.0%)	3 (13.0%)	.090
1st UTI with *E coli*	10 (37.0%)	12 (52.2%)	.283
Retransplantation	0 (0.0%)	1 (4.3%)	.460
Complex renal cyst	3 (11.1%)	6 (26.1%)	.270
Renal calculi	2 (7.4%)	10 (43.5%)	.003
D-J cath–insertion	4 (14.8%)	6 (26.1%)	.480
Ureteral stricture	2 (7.4%)	5 (21.7%)	.225
Technical complications with ureteral anastomosis	2 (7.4%)	2 (8.7%)	1.000
VUR	1 (3.7%)	4 (17.4%)	.167
DM	9 (33.3%)	14 (60.9%)	.052
Urine culture positive at 1st UTI	18 (66.7%)	19 (82.6%)	.200
Graft loss	0 (0.0%)	2 (8.7%)	.207
Azotemia at 1st UTI diagnosis	14 (51.9%)	11 (47.8%)	1.000

Lim JH et al. *Transplantation Proceedings, 2013:45, 1584–1589*

Table 1. Risk Factors for Posttransplant UTI and Recipient and Donor-Related Variables

Variable	UTI Group (n 36)	Control Group (n 69)
Risk factor		
Recipient age, y	51.3 ± 12.3	46.2 ± 10.0*
Recipient gender (male: female)	20:16	47:22*
No. of pretransplant pregnancies	2.7 ± 1.6	1.8 ± 1.3*
Pretransplant PSA, mg/dL	1.0 ± 0.6	1.0 ± 0.8
Posttransplant hospitalization, d	18.8 ± 15.1	16.4 ± 9.8
Acute rejection, %	27	10.1*
Change in prophylaxis, %	44.4	30.4
Donor-related factors		
Donor age, y	38.1 ± 12.9	40.2 ± 13.1
Serum creatinine, mg/dL	1.2 ± 0.6	1.2 ± 0.9
Intensive care unit length of stay, d	7.3 ± 13.4	4.9 ± 3.8
Brain death etiology (trauma: stroke)	19:17	37:32
UNOS expanded criteria, %	36.1	20.2*

Unless otherwise indicated, data are expressed as mean values ± SDs.

Abbreviations: PSA, prostate-specific antigen; UNOS, United Network for Organ Sharing; UTI, urinary tract infection.

*$P < .05$.

Camargo LF et al. Transplantation Proceedings; 2014(46), 1757-1759

Table 2. Risk Factors for Recurrence of Posttransplant UTI

Risk Factor	Isolated UTI (n − 20)	Recurrent UTI (n − 16)
Recipient age, y	52.3 ± 12.0	50.1 ± 13.0
Donor age, y	37.3 ± 14.0	39.2 ± 11.7
Donor creatinine, mg/dL	1.3 ± 0.6	1.1 ± 0.5
Donor ICU stay, d	10.1 ± 19.1	3.9 ± 2.2
Posttransplant hospitalization, d	14.2 ± 5.4	22.8 ± 21.1*
Pretransplant total PSA, ng/dL	0.9 ± 0.5	1.8 ± 0.6*
No. of pretransplant pregnancies	2.3 ± 1.5	3.0 ± 1.7

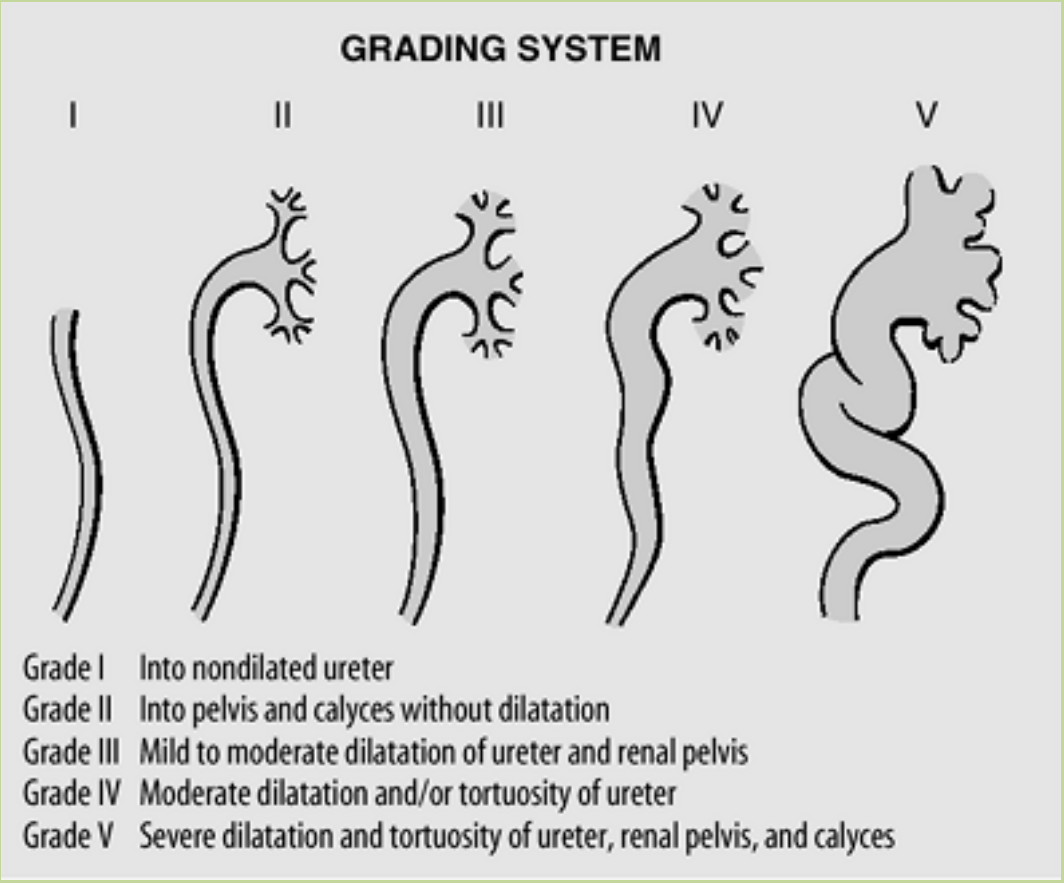
Data are expressed as mean values ± SDs.

Abbreviations: ICU, intensive care unit; PSA, prostate-specific antigen; UTI, urinary tract infection.

*$P < .05$.

Camargo LF et al. Transplantation Proceedings; 2014(46), 1757-1759

Recurrent UTI



- Vesicoureteric reflux (VUR) could possibly a risk for recurrent UTI
- Micturation cystourography could demonstrate the degree of VUR

Macfarlane. Urology, 4th Edition

Recurrent UTI

- Surgical intervention of VUR
  - Open
    - Reimplantation
  - Endoscopic
    - Injection of bulk forming material
- Antibiotics prophylaxis

Recurrent UTI

- Endoscopic treatment
  - N = 58
  - Clinically successful in 32 patients (56.1%)
    - 26 (65%) received dextranomer-hyaluronic acid
    - 5 (33.3%) received polydimethylsiloxane.
    - On multivariate analysis male gender and dextranomer-hyaluronic acid were factors predictive of clinical success.
    - Reflux grade did not predict success or failure.
    - No high grade complication was reported.
    - Repeated injection may be required
    - Obstruction could also possibly happen, requiring open surgical correction

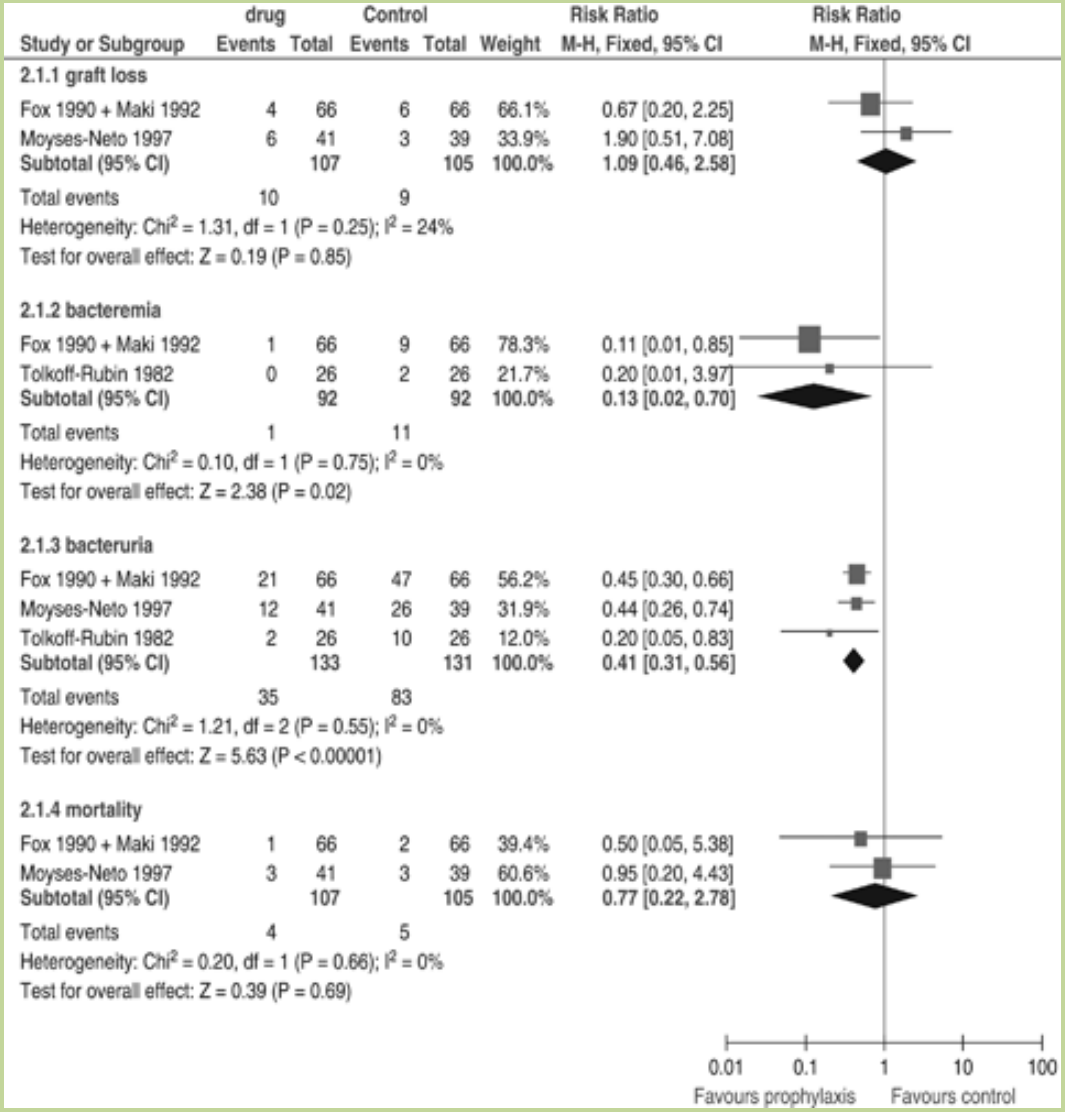
Akiki Akram. The Journal of Urology. January 2015, 193(1), 225–229

Recurrent UTI

- Antibiotics prophylaxis
  - A meta-analysis included six trials
  - N = 545 patients.
  - No significant difference was seen in graft loss (risk ratio [RR] 0.99, 95% confidence interval [CI] 0.91–1.81).
  - Prophylaxis lowered the risk for developing sepsis with bacteremia by 87% (RR 0.13, 95% CI 0.02–0.7) and the risk for developing bacteriuria (symptomatic or asymptomatic) by 60% (RR 0.41, 95% CI 0.31–0.56; 3 trials).
  - No significant reduction was found in all-cause mortality and adverse events rates
  - Conflicting results were reported for the development of resistant bacteria.

Green H. Transplant Infectious Disease. 2011, 13(5), 441-447

Antibiotic prophylaxis for urinary tract infections in renal transplant recipients: a systematic review and meta-analysis



Green H. Transplant Infectious Disease. 2011, 13(5), 441-447

Recurrent UTI

- Antibiotics prophylaxis
  - Kdigo guideline recommended use of TMP-SMX as prophylaxis
  - Minimum of 6 months post transplant.
  - For patients who are allergic to TMP-SMX, the recommended alternative agent would be nitrofurantoin.
- Reduction in immunosuppressive treatment should always be considered
- If no correctable risk factors identified or could possibly amended, we should consider using prophylactic antibiotics indefinitely.


End