



WEST AUSTRALIAN INDIGENOUS KIDNEY TRANSPLANT INFECTION DATA, AND SUMMARY OF BK NEPHROPATHY

Improving Indigenous Kidney Transplant
Outcomes, Darwin 2013

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SUMMARY

- W.A. indigenous kidney transplant infections
 - Screening data
 - Infection data
 - Invasive Fungal Infections
- BK nephropathy
 - Epidemiology
 - Diagnosis
 - Treatment



W.A. INDIGENOUS KIDNEY TRANSPLANT INFECTION DATA

- 2005-2012
- 57 ATSI patients transplanted
- 33 from the Kimberley or Pilbara
- Microbiology results examined for all patients

W.A. SCREENING DATA

Organism	Kim/Pil (n=33) tested (%)	Kim/Pil positive of tested (%)	Non Kim/Pil (n=24) Tested (%)	Non Kim/Pil Positive of Tested (%)	Overall (n=57) Tested (%)	Overall Positive of Tested (%)
HTLV	3	0	4	0	3	0
HBV	100	36 core	100	17	100	26 core
HIV/HCV	100	0	100	0	100	0
HBsAb	94	65	83	55	89	61
TPPA	30	50	21	40	26	47
Strongyloides	30	20	8	100	21	33
VZV	76	100	83	100	77	100
EBV	85	100	92	100	88	100
CMV	100	100	96	96	98	98
Toxoplasma	9	33	12	33	10	33
MRSA	33	73	33	66	30	70



INFECTIONS

Site	Kim/Pil (n=33) Positive Number (%)	Non Kim/Pil (n=24) Positive Number (%)	Overall (n=57) Positive Number (%)
Bacteriuria	16 (48), mean 4 per patient infected	20 (83) mean 3.8 per patient infected	37 (65), mean 4.0 per patient infected
Collection	6 (18)	0 (0)	6 (10)
Bacteremia	4 (12)	8 (33)	12 (21)
Wound	2 (6)	3 (12)	5 (9)
Pneumonia	8 (24)	5 (21)	13 (23)
SSTI	8 (24)	4 (17)	12 (21)



RESISTANT BACTERIURIA

- 5 patients (8.7%) bacteriuria with ESBL E coli
- 8 (14%) with Timentin R E coli



INVASIVE MOULD INFECTION

- 8 cases (14%)
- 2 cryptococcal meningitis, 5 invasive aspergillosis, 1 zygomycosis/aspergillosis
- 3 died
- Cryptococcus 10 months and 4 years post Tx
- IA/Zygo all 2-3 months post Tx
- 3 from Kimberley/Pilbara



INVASIVE FUNGAL INFECTION

- 1. Cryptococcus neoformans meningitis
 - KW 55 y.o. Lady from Perth, DM, vasculopathy, underlying IgA nephropathy, transplant 30/3/08
 - Cryptococcal meningitis diagnosed 21/1/09 (10 months post Tx) given 2-3 weeks amphotericin/5-FC then fluconazole 400mg daily. No prior rejection
 - Died 28/7/10 nine days after presenting with non compliance, renal impairment with rejection, given methylpred, and HAP.



INVASIVE FUNGAL INFECTION

- 2. Cryptococcal meningitis
 - NM 58 y.o. lady from Nullagine Transplant 23/2/09 for DM/HT
 - Presented October 2013 with cryptococcal meningitis
 - No rejection.



INVASIVE FUNGAL INFECTION

- 3. Invasive Aspergillosis
 - JC 45 year old man from Fitzroy Crossing, Underlying chronic GN. Transplant 4/9/2008
 - 6/11/08 Presented with bilateral cavitating lung lesions, culturing *Aspergillus fumigatus* from sputum, treated with voriconazole with improvement
 - CXR pretransplant NAD and no obvious prior lung disease on CT chest
 - No rejection
 - *Strongyloides* in stool 16/10/08



INVASIVE FUNGAL INFECTION

- 4. Invasive Aspergillosis
 - SD 53 y.o. lady from Perth, underlying HT, DM. Transplant 29/8/08
 - 3/11/08 Presented multiple nodular lesions CT chest. Aspergillus fumigatus grown from sputum. Treated voriconazole. Patient improved
 - Possible humoral rejection on biopsy 21/10/08. No previous CXR change or prior lung disease CT chest. History of asthma.
 - Genital CMV 29/1/09



INVASIVE FUNGAL INFECTION

- 5. Invasive Aspergillosis
 - SS 47 y.o. man from Perth. Underlying DM, Transplant 31/1/09
 - 3/3/09 Presented with chest pain SOB, bilateral nodules on CT, Aspergillus fumigatus from sputum and lung biopsy. Treated voriconazole and improved
 - No rejection or prior lung disease



INVASIVE FUNGAL INFECTION

- 7. Invasive Aspergillosis
 - LY 48 y.o. from Geraldton, Transplant 14/10/09 for IgA nephropathy. Alcoholic cirrhotic, DM
 - CT nodules and Aspergillus fumigatus sputum 15/1/10. Died
 - No rejection or underlying lung disease



INVASIVE FUNGAL INFECTION

- 8. Invasive zygomycosis and aspergillosis
 - CH 34 y.o. Lady from Broome. Transplant 19/1/11 for DM.
 - Presented 19/4/11. Pulmonary nodules with infarction. Rhizopus microsporus and Aspergillus fumigatus from BAL. Died 6/5/11
 - Methylpred for rejection in March 2011



OTHER INFECTIONS

- 7 Dermatophyte infections
- GI infections: 4 Cryptosporidium, 2 Isospora, 2 Giardia, 1 Strongyloides intestinal infection, 2 C. difficile, 1 Non Typhoidal Salmonella, 2 Norovirus, 1 Rotavirus.
- Viral infections: 3 Influenza, 5 HSV, 3 CMV (13 CMV viremia), 1 VZV.
- 2 Nocardia (17 months and 15 months post transplant)
- 2 Scabies
- 18 (31%) urine BK positive, 17 (30%) plasma BK positive, 3 (5.3%) BK nephropathy on biopsy



BK INTRODUCTION

- Mean prevalence of BK-nephritis ~5%.
- 85% of patients who develop BK viremia do so within 3-4 months post transplant. Median onset of viruria is 5 weeks and viremia is 10 weeks. Less than 5% of all cases occur 2-5 years post transplant.



BK SCREENING

- Screening and preemptive strategy superior to treating only biopsy proven disease (early action more successful than late action)
- Screening methods:
 - 1. BK viruria
 - Window of 6-12 weeks before viremia and nephropathy
 - High negative predictive value (approaching 100%)
 - Low positive predictive value and 20-60% of patients positive
 - Delayed decline of viral load with reduction in immunosuppression
 - Trigger for action usually $>10^7$ copies/mL*



BK SCREENING

- BK viremia
 - Window period to proven BK nephropathy of 2-6 weeks, therefore more frequent testing (such as monthly screening test) is preferred in some centres
 - Positive predictive value 30-50% for BK nephropathy-higher PPV if high viral load, renal allograft impairment, BK non-coding control region appear in blood, or sustained viremia (e.g. 3 weeks)
 - Trigger for action usually $>10^4$ copies/mL*
- Urine decoy cells
 - Adenov and CMV can cause similar changes, and decoy cells can be absent with virus detected by PCR
- Haufen by EM of urine
 - High PPV and NPV however not widely available



SCREENING FREQUENCY

- Suggested screening frequency in review articles:
 - 3 monthly up to 2 years post transplant, plus when allograft dysfunction or if allograft biopsy performed (Brennan and Ramos; UpToDate).
 - 3 monthly up to 2 years, then annually to 5 years (Hirsch and AST; Am J Transpl 2013).
 - Monthly for 3 months, then test at 6 months and 12 months (Brennan and Randhawa; Am J Transpl 2006).
 - Early intense monitoring of monthly for 3-6 months, then 3 monthly til the end of the first transplant year, and with unexplained renal dysfunction, and after treatment of acute rejection (KDIGO Transplant Working Group).



SCREENING REGIMES

- Suggested screening modalities in review articles:
 - 1. Urine decoy cells or urine quantitative PCR. If positive, confirm within 4 weeks, perform quantitative plasma PCR. Urine $>10^7$ copies/mL*, plasma $>10^4$ copies/mL* recommend renal biopsy.
 - 2. Plasma viral load above threshold*. If creatinine elevated perform renal biopsy and management dictated by findings. If creatinine not increased over baseline, reduce immunosuppression and monitor plasma viral load.
- Literature suggests monitoring of presumptive or proven PyVAN suggested as plasma viral load with intervals of 2-4 weeks.



DEFINITIVE DIAGNOSIS

- Definitive diagnosis by histology demonstrating cytopathic changes (inclusion bodies, tubular injury, tubulitis, interstitial fibrosis) PLUS positive IMC to BK or SV40. Caveats include:
 - (a) focal involvement of kidney leading to suggestion of at least 2 core biopsies, including medullary tissue (BK virus more often present at this anatomical site)
 - (b) possibility of concurrent BK nephritis and rejection
 - (c) histological changes not pathognomonic
Graded by extent of inflammatory infiltrates and interstitial fibrosis



MANAGEMENT

- Reducing immunosuppression effective in 85%
- Switching
 - TAC to CSA or SIR
 - MMF to SIR or LEF
- Decreasing
 - TAC trough <6 ng/ml
 - CSA trough 100-150 ng/ml
 - MMF <1g/day
- Discontinuing
 - TAC or MMF
 - Other
- Antiviral approaches
 - Cidofovir
 - IVIG
 - Quinolone
 - Leflunomide



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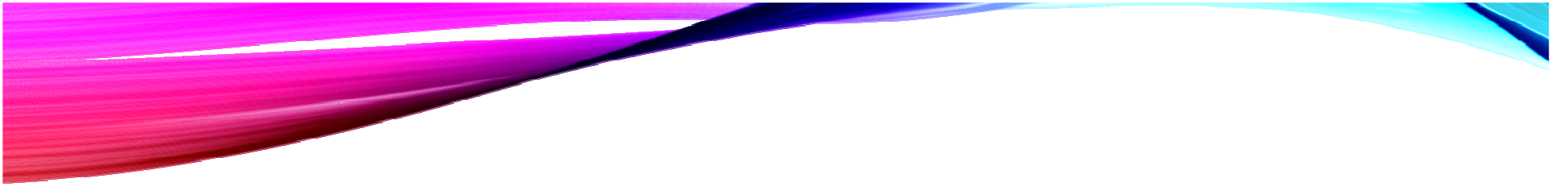
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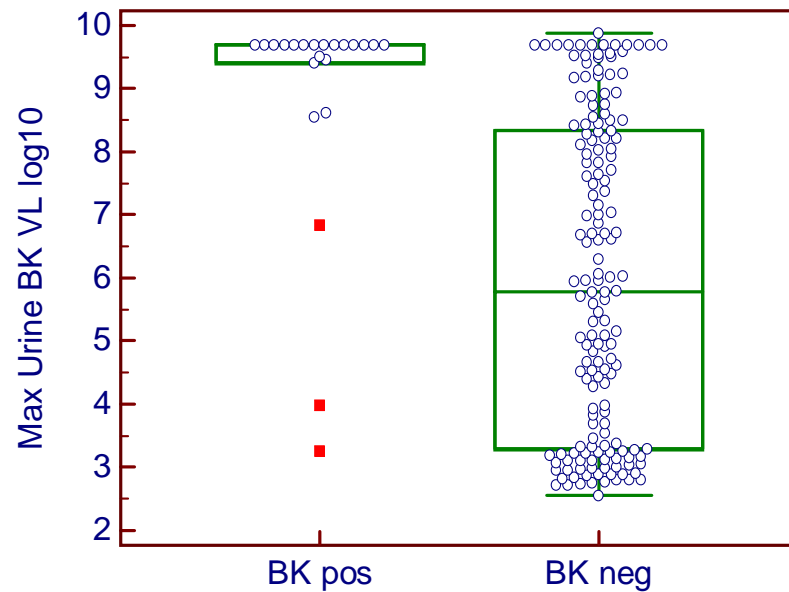
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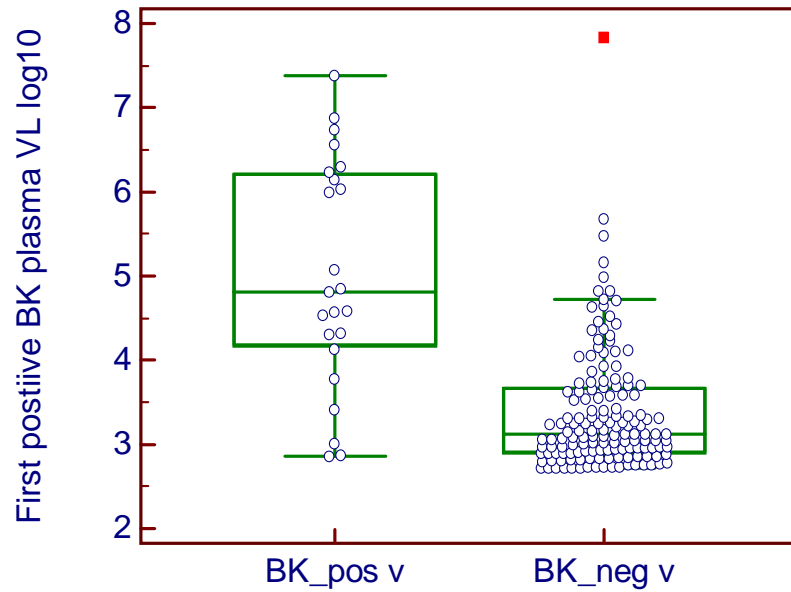
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URINE BK POSITIVE

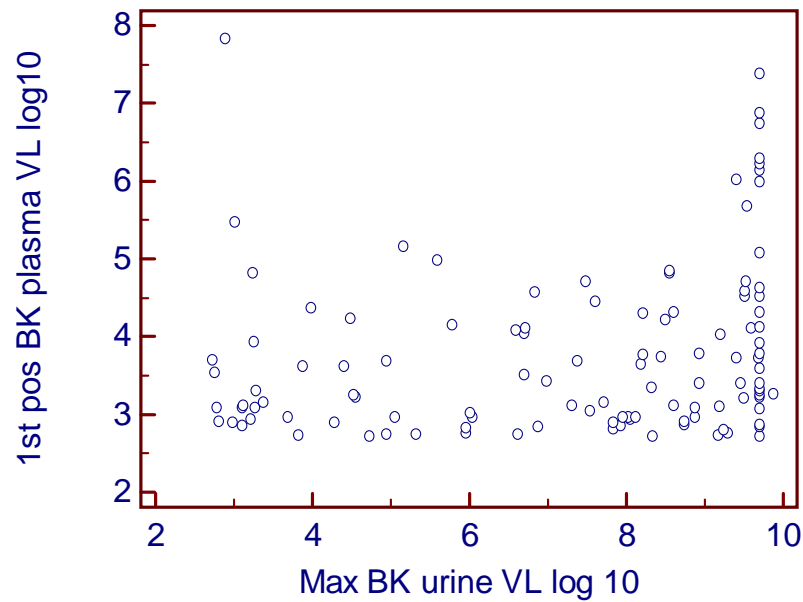


- BK pos 95% CI
9.4614 to 9.6990
- BK neg 95% CI
4.9510 to 6.6939
- $P < 0.001$



- BK pos 95% CI
4.3154 to 6.1074
- BK neg 95% CI
3.0515 to 3.2504
- $P < 0.001$

MAXIMUM VIRURIA AND 1ST VIREMIA



- Correlation coefficient 0.1959, 95% CI 0.01327 to 0.3659
- P=0.03