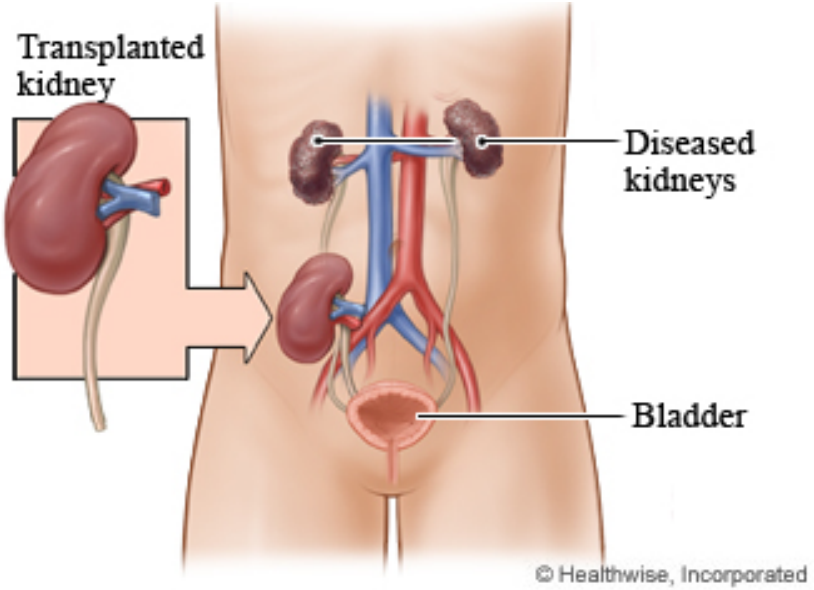
The renal transplant patient in Primary Care



Dr Jyoti Baharani 08/02/16

NHS

HEART of ENGLAND NHS Foundation Trust

BIRMINGHAM HEARTLANDS 50 Years of Dialysis

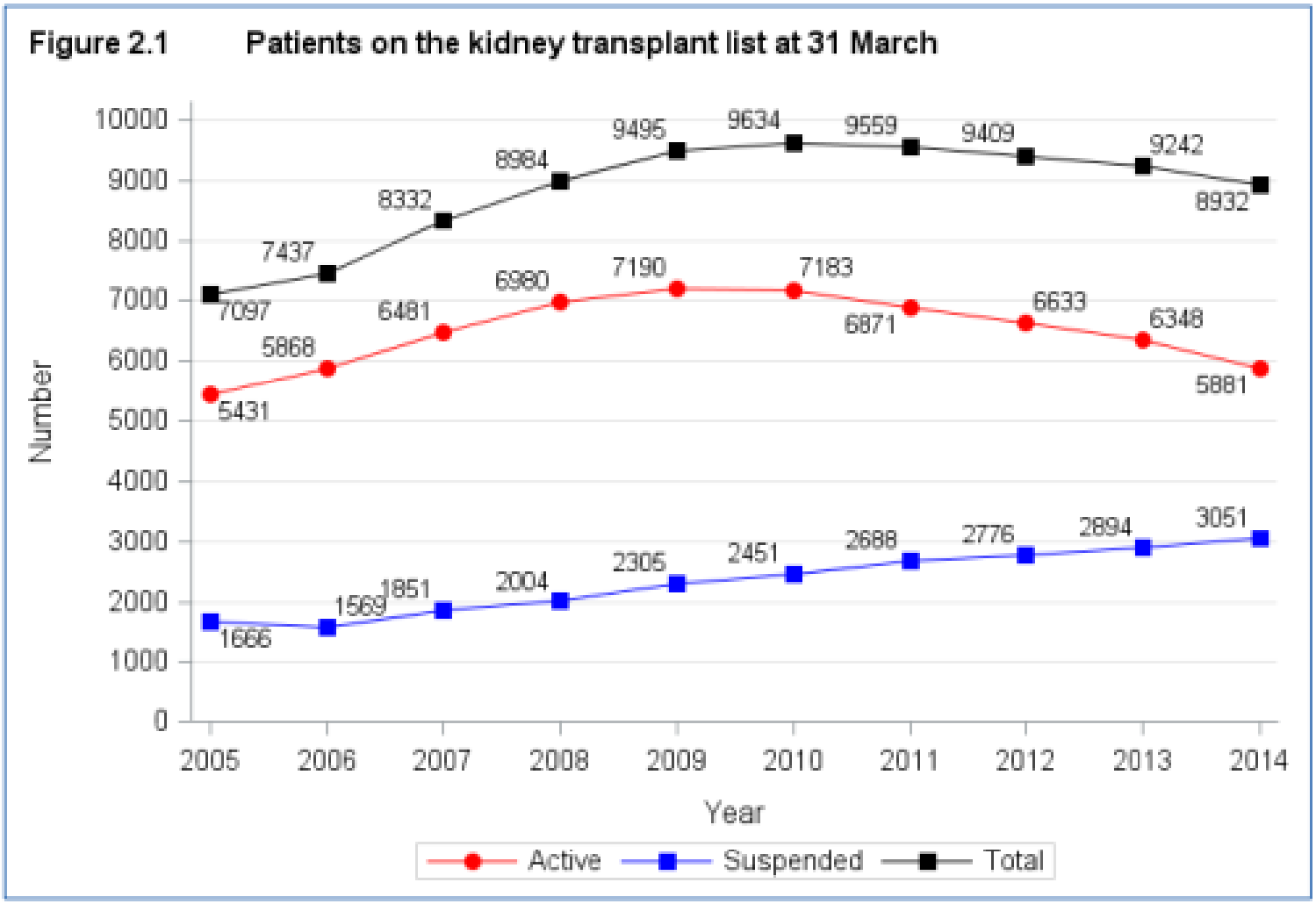
Aims of the talk

- Kidney Transplantation and CKD
- Immunosuppressive Medications and Drug interactions
- Travel and Vaccines
- Cardiovascular Disease Risk Reduction
- New-Onset Diabetes After Transplant
- Cancer
- Fertility
- Bits and bobs

CKD vs. Transplantation

- First renal transplant in the UK 1958
- 25% of patients with on dialysis will be suitable for a kidney TX
- TX offers better survival, QOL and social independence
- the first year of care after a kidney transplant costs around £17,000 and £5,000 for every subsequent year; whereas the average cost of dialysis is £30,800

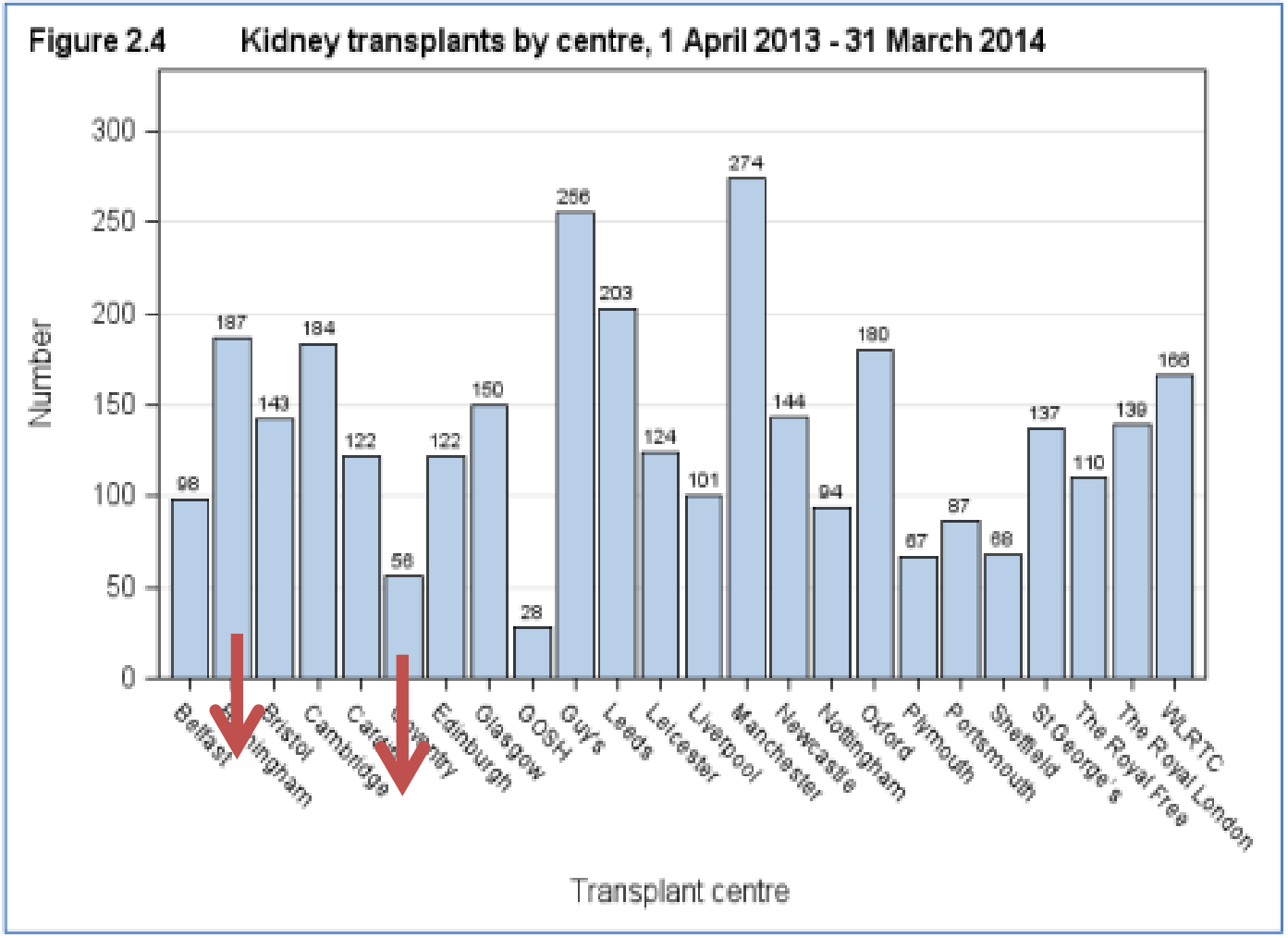
Renal Transplantation in the UK



- There are 20 adult kidney transplant centres in England.
- 6000 patients were on the active list for a kidney only transplant in 2015 (another 3000 suspended)
- 3000 adult kidney only transplants are performed pa in the UK
- 25% are from living donors

- 75% are from cadaveric donors
- Most cadaveric kidneys come from Donation after Circulatory Death (DCD) donors but some from Donation after Brainstem Death (DBD) donors

Number of Kidney transplants in the West Midlands pa



How long is the wait for a DD kidney for your patient?

Table 3.1 **Median waiting time to kidney only transplant in the UK, for adult patients registered 1 April 2008 - 31 March 2011**

Transplant centre	Number of patients registered	Waiting time (days) Median	95% Confidence interval
Adult			
Cambridge	367	572	491 - 653
Plymouth	168	599	510 - 688
Newcastle	261	694	608 - 780
Cardiff	249	747	652 - 842
Leeds	365	799	733 - 865
Liverpool	290	805	695 - 915
Oxford	303	852	795 - 909
Nottingham	241	863	761 - 965
The Royal London	280	988	893 - 1083
The Royal Free	264	1043	904 - 1182
Guy's	412	1060	974 - 1146
Manchester	528	1138	1036 - 1240
Edinburgh	200	1149	1024 - 1274
Glasgow	263	1162	1083 - 1241
St George's	268	1180	1070 - 1290
Coventry	95	1205	1108 - 1302
Portsmouth	231	1245	1173 - 1317
Sheffield	185	1285	1059 - 1511
Bristol	324	1322	1199 - 1445
WLRTC	457	1386	1246 - 1526
Belfast	126	1631	1363 - 1899
Birmingham	570	1735	1650 - 1820
Leicester	269	1768	1556 - 1980
UK	**6716**	**1082**	**1055 - 1109**

Immunosuppresants

- Most transplant patients will require maintenance immunosuppression with at least two agents from different classes
- Potential interactions with these drugs are an important consideration when prescribing, as significant harm can arise from this
- Immunosuppressant's must never be stopped, unless directed by a renal physician

Calcineurin inhibitors (CNI)

- Cyclosporine and Tacrolimus
- . When calcineurin inhibitors bind to intracellular proteins called immunophilins, they block the effect of calcineurin
- This results in reduced production of interleukin-2 and reduced proliferation of T-cells.
- IL2 mediates the process of acute rejection

Cyclosporine

- monitored by trough levels
- Individual patients will have their own target levels, but as a general rule (for patients who are >12 months post transplant), we aim for levels between 50 - 100 ng / ml
- There are 2 formulations available – Neoral and Sandimmune
- These cannot be used interchangeably.
- Side effects include gum hypertrophy, hirsuitism, renal impairment and hypertension

Tacrolimus

- also monitored by trough levels
- As a guide (for patients who are >12 months post transplant), we aim for levels between 5 – 8 ng / ml
- A number of formulations are available – Prograf, Advagraf and Adoport
- These cannot be used interchangeably
- Side effects include hypertension, tremor, susceptibility to diabetes and renal impairment

Anti-proliferative agents (Azathioprine and Mycophenolate)

- act by reducing the proliferation of lymphocytes, thereby reducing susceptibility to rejection
- Levels are not monitored
- Side effects include leucopoenia, bone marrow suppression, skin rashes and hair loss

MMF

- Mycophenolate also acts by inhibiting the DNA synthesis of lymphocytes
- 2 different formulations are available – mycophenolate mofetil and mycophenolate sodium
- These cannot be used interchangeably.
- Although therapeutic drug monitoring is available, levels are not commonly used to determine dosage
- Common side effects include diarrhoea and electrolyte disturbances (hypomagnesaemia, hypokalaemia and hypocalcaemia).

Others

- Sirolimus is not a calcineurin inhibitor.
- acts by inhibiting the response to IL-2 (rather than the production as with the calcineurin inhibitors)
- Sirolimus is monitored by trough levels.
- As a guide (for patients who are >12 months post transplant), we aim for levels between 5 – 8 ng / ml
- Side effects include skin problems (such as acne), proteinuria, anaemia, delayed wound healing, lung problems (interstitial pneumonitis) and predisposition to diabetes

Steroids

- Generally, due to side effects, if patients require long term steroid therapy we aim to minimise the dose to 5mg daily (from a starting dose of >40 mgs)
- This dose may need to be increased temporarily at times of physiological stress (such as surgery or acute sepsis)
- Side effects include osteoporosis, predisposition to diabetes, truncal weight gain, skin thinning, easy bruising, glaucoma and cataracts

Important drug interactions / drugs to avoid

Drug or substance to avoid	Interaction	Reason
NSAIDs (including topical)	NA	Risk of Acute Kidney Injury (AKI)
Gentamicin	NA	Risk of AKI
Macrolide antibiotics (eg erythromycin, clarithromycin)	CNIs (ciclosporin and tacrolimus) and sirolimus	Drug toxicity and AKI
Allopurinol	Azathioprine	Drug toxicity and severe blood dyscrasias
Diltiazem	CNIs and sirolimus	Drug toxicity and AKI
"Azole" anti fungal agents (eg fluconazole)	CNIs and sirolimus	Drug toxicity and AKI
St John's Wort	CNIs and sirolimus	Sub-therapeutic levels and risk of acute rejection
Grapefruit and pomegranate	CNIs and sirolimus	Drug toxicity and AKI
Anti-epileptics (carbemazepine and phenytoin)	CNIs and sirolimus	Sub-therapeutic levels and risk of acute rejection
Certain statins	Ciclosporin	Myositis, drug toxicity and AKI
Rifampicin	CNIs and sirolimus	Sub-therapeutic levels and risk of acute rejection

TOXICITY PROFILES OF IMMUNOSUPPRESSIVE MEDICATIONS

Adverse effect	Steroids	CsA	Tac	mTORi	MMF	AZA
New-onset diabetes mellitus	↑	↑	↑↑	↑		
Dyslipidemias	↑	↑		↑↑		
Hypertension	↑↑	↑↑	↑			
Osteopenia	↑↑	↑	(↑)			
Anemia and leucopenia				↑	↑	↑
Delayed wound healing				↑		
Diarrhea, nausea/vomiting			↑		↑↑	
Proteinuria				↑↑		
Decreased GFR		↑	↑			

AZA, azathioprine; CsA, cyclosporine A; GFR, glomerular filtration rate; MMF, mycophenolate mofetil; mTORi, mammalian target of rapamycin inhibitor(s); Tac, tacrolimus.

↑ indicates a mild-moderate adverse effect on the complication.

↑↑ indicates a moderate-severe adverse effect on the complication.

(↑) indicates a possible, but less certain adverse effect on the complication.

Non-adherence to medications

- Nonadherence behavior prior to transplantation
- Psychiatric illness
- Personality disorders
- Poor social support
- Substance abuse and other high-risk behavior
- Adolescence
- High education level
- Time since transplantation (higher earlier)
- Lack of adequate follow-up with transplant specialists
- Inadequate pretransplant education
- Multiple adverse effects from medications
- Complex medication regimens

Infections

- infections in kidney transplant recipients are a common occurrence
- Treatment with antibiotics should take account of potential interactions with immunosuppressants
- Transplant recipients are also susceptible to “atypical” infections such as cytomegalovirus (CMV)

Respiratory tract infections

- Should be treated in the same manner as in patients who are not immunocompromised
- Antibiotics that interact with immunosuppressant's (such as clarithromycin and erythromycin) should be avoided
- Due to the possibility of atypical infection, or other causes for symptoms, there should be a low threshold for arranging imaging, such as a chest X-ray

Urinary tract infections

- Should be treated if symptomatic
- Often, if patients are asymptomatic, patients are not treated, but advice should be sought from the renal unit
- antibiotics such as trimethoprim should be avoided if possible (elevates serum creatinine) as should nitrofurantoin should be avoided if eGFR < 60)

Varicella

- Shingles should be treated with aciclovir (dose adjusted for renal function) for seven days
- inform the renal team before starting treatment as there is a risk of interaction with ciclosporin
- Additionally anti-proliferative agents may need to be held temporarily
- Chicken pox is a medical emergency
- This can still occur in transplant recipients who have previously demonstrated immunity or who have been previously vaccinated.
- admission to hospital and isolation usually needed
- Treatment is with intravenous aciclovir and possibly intravenous immunoglobulin

Cytomegalovirus (CMV)

- Symptoms of CMV disease include fever, leucopenia, or organ involvement (including hepatitis, pneumonitis, pancreatitis, gastritis, colitis, meningoencephalitis, myocarditis and chorioretinitis)
- symptoms can be non specific (eg weight loss) and may not, at first, be attributed to CMV
- Diagnosis is by CMV PCR.
- Treatment is with valganciclovir, and should only be initiated by the renal team

Vaccinations and travel

- Transplant recipients **will be immunosuppressed, so some vaccines will be unsuitable** (eg live vaccines)
- Wherever possible, potential recipients should be vaccinated before transplantation, especially for vaccines that would be contraindicated in the post transplant period (eg varicella)
- For the transplant recipient who wishes to travel, they should be encouraged to visit a travel clinic beforehand
- Prophylactic anti-tuberculous therapy is not recommended for travel to high risk areas

- Generally we advise transplant recipients to avoid foreign travel in the first three months post transplant until transplant function is entirely stable
- After this period has elapsed and transplant function is stable the renal transplant patient can travel virtually anywhere in the world
- travel to under-developed countries is not without risk
- Disease like cryptosporidium can result in self-limiting diarrhoea in an immunocompetent host however in an immunosupressed transplant patient they can be life threatening

Vaccines in renal TX patients

Safe vaccines	Contraindicated vaccines
Pneumococcal	MMR (measles, mumps and rubella), or given as individual vaccines
Hepatitis A	Polio (live oral)
Hepatitis B	Yellow fever
Tetanus toxoid	Varicella
Haemophilus influenzae B (HIB)	BCG
Meningococcus	Typhoid (live oral)
Polio (killed)	
Diphtheria	
Pertussis	
Influenza	
Typhoid (killed)	

CV risk reduction

- The most common cause of death in renal transplant recipients is now cardiovascular disease
- risks are much elevated compared to the general population and the prevalence of cardiovascular disease approaches 20 % post transplant
- Managing risk factors such as hypertension, diabetes, dyslipidemia, and cigarette smoking is a major priority in the long term follow up of renal transplant patients

Hypertension

- The prevalence of arterial hypertension is high, up to 50% in renal transplant recipients
- Follow BHS guidelines for renal TX patients
- There is no particular evidence to support any one agent
- Diltiazem should be avoided in patients taking tacrolimus, ciclosporin or sirolimus (risk of interaction)

- We do use ACE inhibitors and ARB's especially if the patient remains proteinuric
- Best avoided in --the early post transplant period when renal function is unstable
- If a transplant patient has resistant hypertension consideration should be given to whether they have a transplant RAS

PTDM/NODAT

- Particular attention is given to screening for Post-transplant diabetes which is very common given the steroid use and a known side effect of tacrolimus
- A dipstick urine for glucose and a fasting glucose should be checked at every opportunity
- Post-transplant diabetes should be managed in conjunction with a specialist in Diabetes but again treatment targets are similar to that for T2DM

- We also measure fasting lipids at least annually to detect and treat hyperlipidaemia which has the same targets and treatment as the general population
- We encourage all transplant recipients to adopt a healthy lifestyle including smoking cessation, maintaining a healthy body weight and avoidance of excessive alcohol

Cancer

- major cause of both morbidity and mortality in renal transplant recipients
- Transplant recipients are at an increased risk for the development of skin and solid organ malignancies and lymphoma (post transplant lymphoproliferative disease or PTLD)
- No additional screening outside national guidelines is currently advised for transplant recipients, but attention should be paid to any symptoms suggestive of malignancy and there should be a low threshold for further investigation
- Transplant recipients should be actively encouraged to attend screening test appointments (cervical, breast and colon)

Contraception

- Reproductive function is usually impaired in patients receiving dialysis but this is usually restored after transplantation
- It is, therefore, important that patients receive adequate counselling about effective contraception in the post-transplant period to avoid unplanned pregnancies.
- All contraceptive agents are safe to use in transplant recipients, although progesterone could interact with tacrolimus and ciclosporin

- CNI's and MMF also reduce efficacy of the oral contraceptive pill
- For transplant recipients who are planning to conceive, immunosuppression may need modification beforehand
- This should only be done by the renal unit
- Both MMF and sirolimus are contraindicated in pregnancy
- Pregnancy in transplant recipients should be co-managed by a centre that is familiar with the management of such patients

Transplant bone disease

- The risk of fractures following kidney transplantation is high
- Bone disease is multifactorial, and most patients will have pre-existing CKD-MBD
- Treatment with calcitriol, alfacalcidiol, or vitamin D has been suggested to improve BMD

Hyperuricemia and gout

- Hyperuricemia is common
- increases the incidence of gout and may be associated with loss of kidney function and CVD
- Treat hyperuricemia when there are complications, such as gout, tophi, or uric acid stones
- colchicine for acute gout, with appropriate dose reduction for reduced kidney function and concomitant CNI use
- avoid allopurinol in patients receiving azathioprine

Mental health

- Depression and anxiety are more common than in the general population
- May be associated with medication nonadherence, sleep disorders, and other adverse effects
- direct questioning about depression and anxiety are part of routine follow-up care after kidney transplantation

Graft and patient survival

- The national rate of graft survival five years after first adult DD kidney only transplant is 86%
- The national rate of ten year patient survival from listing for DD kidney only transplants in adult patients is 75%

If you require help or advise please contact the Kidney failure support team on 0121 424 677, the on call renal registrar or consultant

Many thanks

Jyoti.baharani@heartofengland.nhs.uk

@renalpages