The Renal Transplant Patient

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Introduction

- Renal transplantation is the preferred treatment for patients with end-stage renal disease. It offers better quality of life and confers greater longevity than long-term dialysis.

- EMPs encounter transplant pts at 2 critical stages:
- Initial doctors to identify potential donors from a pool of critically ill patients who are admitted to hospital.
- They care for pts once they have been transplanted and present with complications related to their immunosuppressive therapy, infections or ARF.

- Diabetic nephropathy accounts for 40% of the diseases resulting in renal transplantation. This subgroup of pts are also more prone to complications after renal transplantation.
- The spectrum of diseases in transplant pts is different from the general population.
- The classical presentation of common medical disorders may be modified by immunosuppressive medication.

The Transplantation Process

- Transplant coordinators should be called early for any pt who may meet brain death criteria in the new future.
- Absolute C/Is for organ donation include HIV, sepsis, non-CNS malignancy and severe CVS disease.
- Age is also a relative C/I (i.e. organs not harvested from pts >75 years of age).
- The pretransplantation workup of a potential donor includes testing for CMV, HSV, EBV, HIV, Hep A, B, C, D + E and HTLV type 1.

- Following brain death, a number of physiological changes occur that need to be rectified if donor organ perfusion is to be preserved.
- Increased cerebral oedema after trauma or stroke results in catecholamine release and HT.
- With brainstem necrosis, catecholamine levels drop rapidly resulting in hypotension. This should be corrected with fluid and vasopressors.

- About 75% of organ donors develop diabetes insipidus due to pituitary necrosis and this leads to hypovolaemia.
- Systemic thermal control is often lost due to hypothalamic ischaemia which results in coagulopathy, hepatic dysfunction and cardiac dysfuction.

Definitions

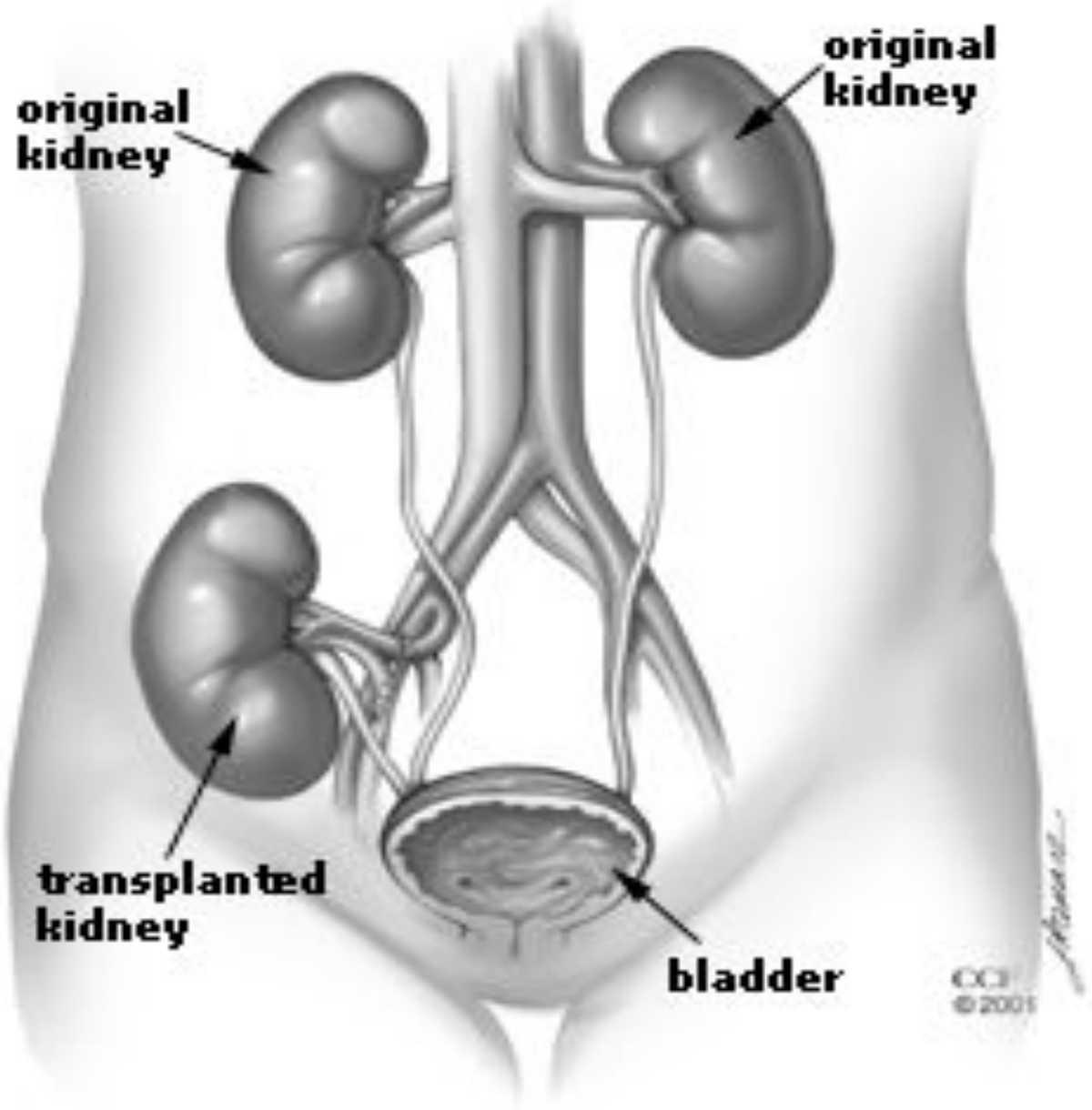
- Allograft : graft between genetically dissimilar individuals of the same species.
- Autograft : graft in which donor and recipient are the same individual.
- Xenograft : Donor and recipient belong to different species.

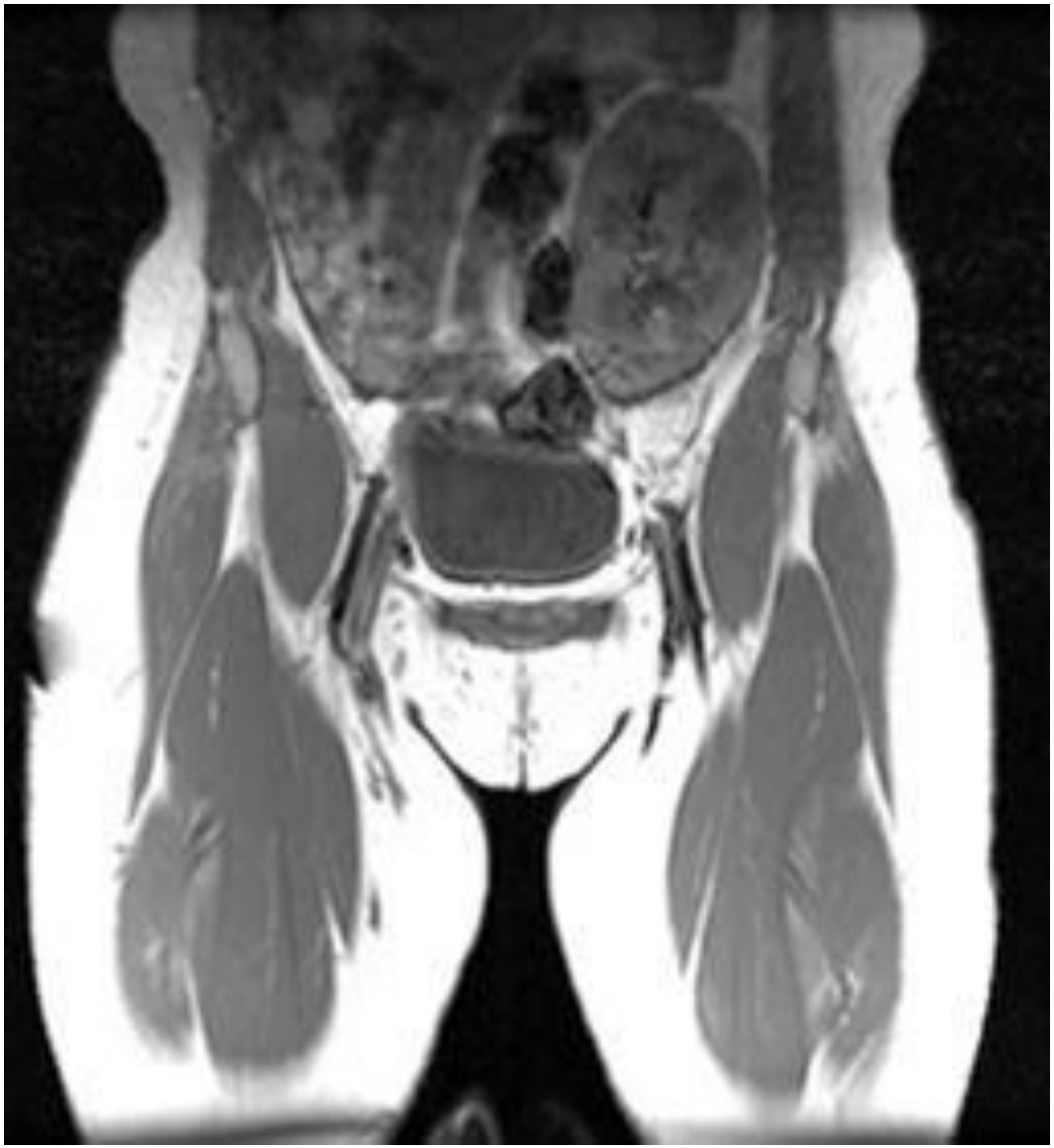
The Surgical Procedure

- Wet ischaemia time (time from cessation of circulation to removal of organ and its placement in cold storage) should not exceed 30 mins.
- Transplanted kidney is placed in the R or L lower quadrant of the abdomen in an extraperitoneal position. On examination, the transplant is easily palpable.

- The transplant renal a is anastomosed to the ipsilateral internal or external iliac a, the renal v to internal or external iliac v and the transplant ureter to the bladder.
- Generally a single kidney is transplanted.
- When small, paediatric or older cadaveric donor kidneys with age-related loss of renal fxn are transplanted, both kidneys from the donor might be placed in a single recipient to provide adequate fxnal renal mass.

- Living donor transplants fxn immediately after transplant, +/- 30% of cadaveric transplants have delayed graft fxn because of more prolonged ischaemic cold preservation. These pts need continued dialysis support until the kidney starts to fxn.


original kidney
original kidney
transplanted kidney
bladder



Graft Prognosis

- Directly related to source of donor kidney.
- Recipients of cadaveric kidneys have more episodes of rejection and lower graft survival rates.
- Graft survival rates for kidneys from living donor is 95% @ 1 yr and 76% @ 5 yrs vs graft survival from a cadaveric kidney donor is 89% @ 1 yr and 61% @ 5 yrs.

Morbidity

- Infection (most common cause of M&M in first year post transplantation) and graft failure occur.
- HT occurs in 75-85% of all renal transplant recipients.
- Hyperlipidaemia 60%
- CVS disease 15.8 – 23%
- DM 16.9 – 19.9% (more likely to be present before transplantation and new onset DM after transplantation is related to corticosteriod use.)

- Osteoporosis 60%
- Malignant neoplasm 14% - related to the degree of immunosupression.

Mortality

- Survival of pts after transplantation from a liver donor is 98% at 1 yr and 91% @ 5 yrs.
- Survival of pts who receive cadaveric organs is 95% @ 1 yr and 81% @ 5 yrs.

Hx of a pt with organ transplant presenting to ED

- Current symptoms (esp. fever)
- Transplant age (interval since transplant)
- Living or cadaveric source
- Previous episodes of rejection
- Current medications (including over the counter preparations)
- Recent medicine changes

- Immunosuppressive Rx
- Compliance with Rx
- Previous infections
- Recent exposure to ill pts

Examination of the Patient

- Inspect, palpate and auscultate the graft site.
- Graft tenderness and swelling is often observed in acute rejection, outflow obstruction, pyelonephritis and renal vein occlusion.
- Bruits are heard in RA stenosis and AV malformations.

Immunosuppressive Therapy

- Renal transplant pts require lifelong immunosuppression to prevent rejection.
- Current “triple” regimes include cyclosporine-microemulsion or tacrolimus, mycophenolate mofetil or azathiopine and corticosteroids.
- Sicrolimus became available in 1994 and has become incorporated into protocols.

- **Cyclosporine**: inhibits both cellular and humoral immunity by binding to cyclophilins which block cytokine transcription and production resulting in the inhibition of lymphocyte signal transduction.

  Results in potent immunosuppression of helper T cells, without affecting suppressor T cells.

- **Azathioprine**: antimetabolite derivative of 6-mercatopurine. Inhibits DNA + RNA synthesis, resulting in suppression of lymphocyte proliferation.
- **Corticosteroids**: wide range of effects on immune system specifically the T lymphocytes. Because of long-term toxic effects, every effort is made to minimise the dosage of glucocorticoids.

- **Tacrolimus**: newer macrolide compound that binds to lymphocyte proteins and inhibits cytokine synthesis. Used as either primary or rescue therapy for allograft rejection.

- Immunosuppressant minimisation protocols are becoming more popular.
- Triple Rx for 3-12 months after transplantation followed by withdrawal of 1 of the 3 drugs to minimise long term side effects (most commonly withdrawn drug is corticosteroid).
- Antilymphocyte Abs are also widely used in the pts (polyclonal & monoclonal Abs are available).

- The initial Rx of rejection involves the administration of IVI corticosteroids (methylpred 250-1000mg daily for 3/7 or dexamethasone 100mg daily for 3/7).

Table 1.

Currently approved maintenance immunosuppressive medications.

Medication	Typical Dose Initial/Maintenance	Target Blood Level (Trough)
Cyclosporine (Sandimmune or generic)	5–6 mg/kg PO Q12; maintenance dose determined by blood level	250–400 ng/mL (initial) 125–200 ng/mL (long term)
Cyclosporine microemulsion (Neoral or generic)	4–5 mg/kg PO Q12; maintenance dose determined by blood level	250–400 ng/mL (initial) 125–200 ng/mL (long term)
Tacrolimus (Prograf)	0.1 mg/kg PO Q12; maintenance dose determined by blood level	10–20 ng/mL (initial) 5–10 ng/mL (long term)
Azathioprine (Imuran or generic)	1.5–2.5 mg/kg PO QD (adjusted for blood counts)	Blood level monitoring not used in clinical practice
Mycophenolate mofetil (CellCept)	1.0–1.5 g PO Q12 (adjusted according to gastrointestinal adverse effects and blood counts)	Blood level monitoring not used in clinical practice
Prednisone, prednisolone, methylprednisolone	0.5 mg/kg/day (initial) 0.1 mg/kg/day (long term)	Blood level monitoring not used in clinical practice
Sirolimus (Rapamune)	2–5 mg PO QD (adjusted according to level)	10–20 ng/mL (initial) 5–15 ng/mL (long term)

PO, By mouth; **Q12**, every 12 h; **QD**, once daily.

Table 2.
Adverse effects of maintenance immunosuppressive medications.

Medication	Adverse Effects
Cyclosporine	Acute (functional) and chronic (structural) nephrotoxicity, hyperkalemia, hypomagnesemia, hyperuricemia/gout, hemolytic-uremic syndrome, hypertension, hyperlipidemia, diabetogenicity, hepatotoxicity, neurotoxicity, hirsutism, gingival hyperplasia
Tacrolimus	Similar to cyclosporine except neurotoxicity (tremors, paresthesias, headache, insomnia, seizures) more common; hair loss (instead of hirsutism), no gingival hyperplasia; more diabetogenic; less hypertension and hyperlipidemia
Azathioprine	Bone marrow suppression, macrocytosis with or without anemia, hepatotoxicity, pancreatitis
Mycophenolate mofetil	Abdominal pain, anorexia, nausea, vomiting, upper gastrointestinal bleeding, diarrhea, anemia, leukopenia, thrombocytopenia
Corticosteroids	Weight gain, Cushingoid appearance, cataracts, acne, thinning of skin, easy bruising, osteoporosis, fractures, avascular necrosis (hip/knee), upper gastrointestinal ulceration/bleeding, diabetogenicity, psychologic effects, hyperlipidemia
Sirolimus	Thrombocytopenia, less commonly leukopenia/anemia; hyperlipidemia; buccal ulceration; diarrhea; interstitial pneumonitis

Table 4.

Drug interactions with immunosuppressive medications.

Immunosuppressive Drug	Interacting Drug	Mechanism of Interaction	Possible Adverse Effect
Drugs metabolized by hepatic cytochrome P-450 enzyme system			
Cyclosporine or tacrolimus or sirolimus	Diltiazem, verapamil, amiodarone, keto-, flu-, or itraconazole, erythromycin, azithromycin, clarithromycin	Inhibition of cytochrome P-450 enzyme system with increased blood level of immunosuppressive drug	Nephrotoxicity caused by increased blood level of cyclosporine, tacrolimus; possible aggravation of other adverse effects of these drugs
Cyclosporine or tacrolimus or sirolimus	Phenobarbital, phenytoin, Carbamazepine, rifampin, isoniazid	Induction of hepatic cytochrome P-450 enzyme system with decreased blood level	Increased risk of rejection because of lower blood level of immunosuppressive drug
Cyclosporine or tacrolimus	HMG CoA reductase inhibitors ("statins")	Statin level increased by immunosuppressive drug	Increased risk of statin-induced rhabdomyolysis
Cyclosporine or tacrolimus	Aminoglycosides, iodinated radio-contrast, amphotericin-B	Combined nephrotoxicity of the immunosuppressive drug and the coadministered drug	Synergistic nephrotoxicity
Azathioprine	Allopurinol	Inhibition of xanthine oxidase by allopurinol decreases uric acid synthesis. Xanthine oxidase inhibition also decreases the metabolism of azathioprine, with resultant increase in azathioprine levels.	Increased azathioprine level causes bone marrow suppression

Surgical Complications affecting Allografts

- Usual postop generic complications: atelectasis, pneumonia, wound infection, ileus, bleeding and venous thromboembolism.
- 1. ***Acute occlusion of transplant renal a or v.***

  Occurs in first transplant week (0.5-8%). Causes oligoanuria and ARF. With renal vein thrombosis, there is graft tenderness, dark haematuria and decreased urine volume.

  Diagnosis is via doppler U/S or radioisotope scanning to demonstrate lack of blood flow.

  Rx is surgery.

- 2. ***Peritransplant haematoma***

  Early postop complication or in setting of perioperative anticoagulation (2-3%)

  Severe pain over allograft, decreased Hb or Hct, increased serum creatinine.

  Recurrent increased K due to lysis of RBC in haematoma.

  Diagnosis via CT.

  Rx is surgical and usually leads to allograft nephrectomy.

- 3. ***Urinary Leak***

  First transplant month. (2-5%)

  Presents with urine extravasation and ARF, fever, pain and distended abdomen.

  Diagnosis is via U/S which demonstrates a peritransplant fluid collection or via radioisotope scanning.

  Treatment is foley catheter insertion and surgery.

- 4. ***Lymphocoele***

  Occurs within the first 3 post transplant months and is due to lymph leaking from severed lymphatics (5-15%).

  Large collections cause pain, ARF, urinary frequency, ipsilateral lower extremity oedema, occasionally iliac vein thrombosis or PE. Most of the s&s are due to pressure effects.

  Diagnosis is via U/S.

  Treatment is percutaneous drainage.

- 5. ***Obstructive Uropathy***

  Occurs in early post transplant period (3-6%). The commonest causes are extrinsic compression of the ureter by a lymphocoele or due to a technical problem with the ureteric anastomosis to the bladder.

  Diagnosis is best achieved via U/S demonstrating hydronephrosis.

  Treatment is surgical.

- 6. ***Renal artery stenosis***

  Late presentation.

  Pts present with uncontrolled HT, allograft dysfunction and peripheral oedema.

  Diagnosis is via U/S or MRA.

Fever in the Transplant Pt

- Commom problem.
- Opportunistic infections occur frequently.
- Remember that fever may be non-infectious.

Infections in the 1st post transplant month

- Usual post op infections: pneumonia, wound infection, line sepsis, UTI secondary to foley catheter.
- Opportunistic infections are uncommon.
- Most common organisms: E.coli (UTI), S.aureus + S.viridans (line sepsis and wound infections) and S.pneumoniae (pneumonia).

Infections in the remainder of the 1st post transplant year

- Opportunistic infections are most common after the first month and then uncommon 6-12 months after transplant.
- CMV (10-25% of recipients).
- CMV disease: fever, elevated LFTs, leukopaenia, anaemia, thrombocytopaenia, arthralgias, myalgias and lymphadenopathy.
- In more severe cases, tissue-invasive CMV infection occurs (pulmonary, upper or lower GIT, CNS).

- Most reliable diagnosis is PCR for viral DNA in blood.
- Untreated CMV has a mortality as high as 15%.
- Bacterial, viral, fungal and protozoan infections are all possible.

Infections after the 1st post transplant year

- Community-acquired infections unrelated to immune suppression are more common.

Non-infectious causes of fever

- Pulmonary atelectasis (early post op)
- Severe acute rejection
- Administration of antilymphocyte Abs
- Post transplant lymphoma

Initial Work-up for febrile post transplant pt

- FBC + diff
- Serum creatinine
- Urine dipstix and analysis
- Urine and blood cultures
- CXR
- Consider transplant U/S
- Additional tests done according to clinical setting

Cardiovascular disorders

- The risk of CVS disease is increased 3 to 5 fold in kidney transplant recipients compared to the general population.
- Atherosclerotic vascular disease accounts for 30-50% of deaths after the first post transplant year.
- Diltiazem, Verapamil + Amiodarone inhibit hepatic cytochrome p450 enzyme system resulting in elevated levels + possible toxicity of cyclosporine, tracrolimus and sirolimus.

HT Complications

- Prevalence is 70-90% in renal transplant recipients.
- None of the parentarel or oral antiHT agents commonly used to Rx severely elevated BP is C/I in these pts.
- Possible aetiologies of HT include: graft rejection, cyclosporine toxicity, glomerulonephritis, graft renal artery stenosis, essential HT from native kidney, hypercalcaemia and steroid use.

Pulmonary Complications

- Most common pulmonary problem is pneumonia.
- Nonopportunistic post op pneumonia in the 1st month, after which opportunistic pulmonary infection takes over.
- After the 1st year, community-acquired infection is common.
- If erythromycin, azithromycin or clarithromycin are used to treat pneumonia, then the dose of cyclosporine, tacrolimus + sirolimus should be reduced for duration of Rx.

GIT Problems

- Abnormalities in LFTs occur frequently.
- The clinical presentation of acute cholecystitis may be blunted by immunosuppressive Rx (esp. by corticosteroid use).
- The incidence and severity of acute pancreatitis is increased.

Neurologic + Psychiatric Disorders

- Cyclosporine and tacrolimus cause similar neurological S/Es (headache, insomnia, tremors, parasthesias, cramp of extremities). The S/Es are dose + blood level related.
- Opportunistic CNS infections occur in 5-10% of renal transplant recipients.

- Meningitis: Listeria monocytogenes, cryptococcus + TB.
- Encephalitis or meningoencephalitis: CMV, toxoplasma or HSV.
- Post transplant lymphoma commonly involves CNS.
- Depression and suicide are more prevalent.
- Remember steroid psychosis.

Haematological Disorders

- Anaemia, leukopaenia, thrombocytopaenia alone or in combination is common. Often due to drugs.
- HUS: anaemia, thrombocytopaenia, ARF, increased LDH, Decreased haptoglobin, schistocytes on peripheral blood smear. HUS in renal transplant pts has been associated with cyclosporine or tacrolimus Rx, acute vascular rejection + CMV infection.

- Post transplant erythrocytosis occurs in 10-20% of pts during the first post transplant year + persists long term in 50% of affected individuals. Venesection may be required + ACE inhibitors or angiotensin II receptor blocker Rx can decrease erythropoiesis.

Musculoskeletal Disorders

- Corticosteroids, and to a lesser extent cyclosporine + tacrolimus predispose to osteoporosis.
- Cyclosporine + tacrolimus cause hyperuricaemia which predisposes to gout.
- NSAIDs can worsen renal fxn + colchicine can interact with cyclosporin causing raised LFTs, leukopaenia, proximal muscle weakness and rhabdomyolysis

- With pts on azothioprine, the use of allopurinol can cause severe bone marrow suppression unless the azothioprine dose is reduced.

Dermatological Disorders

- A variety of disorders can occur: acne,herpes zoster, human papilloma virus, squamous cell Ca (more comman than basal cell Ca), human herpes virus 8 – related KS.

Electrolyte Abnormalities

- Cyclosporin + tacrolimus cause hyperkalaemia (decreased K excretion in urine) and hypomagnesemia (increased Mg excretion in urine).
- Non anion gap metabolic acidosis can be due to tubular dysfunction due to acute or chronic rejection of kidney transplant.

New Onset DM

- De nova DM occurs in 5-20% of renal transplant recipients.
- Contributing to this complication are corticosteroids, cyclosporine + tacrolimus.

Malignancy

- Transplant recipients are at significantly higher risk for cancers than the general population because of (1) chronic immunosuppression, (2) chronic antigenic stimulation, (3) increased susceptibility to oncogenic viral infections, and (4) direct neoplastic action of immunosuppressants. Transplant recipients have a significant overall 2-5 fold higher risk in both sexes for cancers of the colon, larynx, lung, and bladder and in men for cancers of the prostate and testis.

Stress-dose Corticosteroid Coverage

- Severely ill renal transplant pts presenting to ED will require stress-dose corticosteroid coverage (hydrocortisone 50-100 mg IV 6-8 hrly) to avoid acute adrenal insufficiency, unless the pt has not been receiving corticosteroids for > 6-12 months.

Acute Rejection

- Indirect pathway: soluble donor Ag that is processed by recipient APC + then presented to recipient T-cells in the groves of MHC I + II molecules.
- Direct pathway: donor APC presenting both class I + class II epitopes to recipient T cells.
- Hyperacute rejection occurs immediately in the operating room, when the graft becomes mottled and cyanotic. This type of rejection is due to unrecognised compatibility of blood groups A, AB, B, and O (ABO) or a positive T-cell crossmatch.

- Acute rejection appears within the first 3 posttransplant months and affects 30% of cadaveric transplants and 27% of transplants from living donors. Approximately 20% of patients with transplants experience recurrent rejection episodes. Patients present with decreasing urine output, hypertension, rising creatinine, and mild leukocytosis. Fever, graft swelling, pain, and tenderness may be observed with severe rejection episodes.
- The final diagnosis depends upon a graft biopsy.

Chronic Rejection

- Usually apparent from 3 months onwards and detected clinically by gradual deteriation in graft fxn.
- Factors associated with chronic rejection are both immunological + non-immunological.

Take Home Massage

- 1. If a transplant pt presents the ED, always consider the possibility of organ rejection, infection or drug toxicity.
- 2. The signs + symptoms of medical problems are often subtle.
- 3. Inability of the pt to not take their oral immunosuppressants even for one day should be considered an emergency.
- 4. When prescribing in the ED, always be careful to avoid drug interactions + toxicity.

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