

# Caring for transplant patients

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# Case 1: infection

- 65 yo M with PMH significant for LDKT in 2017 , on MMF 1.5 g , Tacrolimus 1.5 mg BID and Prednisone 5 mg , presented to ED with dysuria. BP of 90/60 mmHg, HR of 100. UA: WBC of 118, RBC of 15, pos for bacteria . Uc pending. He has leucocytosis with WBC of 26.000 mg/dl. After 3 L of NS his BP is still 90/60. He is started on Ceftriaxone 2 g and Levophed. What you will do with his immunosuppression:
- A. Hold Tacrolimus and give stress dose steroids
- B. Hold MMF , send tacrolimus level and give stress dose steroids
- C. Hold MMF, Tactrolims and give stress dose steroids
- D. Continue with the same immunosuppression



# Case 2: malignancy

- 70 yo F with DDKT in 2016, on MMF 500 mg BID, Tacrolimus 1 mg BID, presented to the hospital with intractable headache. A CT of the head was done. Patient is found with a brain tumor. What is the best answer regarding this patient tumor:
- A. This is PTLD, patient was EBV neg and he got an EBV pos. Kidney
- B. This is PTLD, patient was EBV neg and he got an EBV negative kidney
- C. This is PTLD, patient was EBV positive and he got an EBV positive kidney
- D. This is PTLD, patient was EBV positive and he got EBV negative kidney
- E. This is PTLD, EBV status does not play a role in incidence of PTLD
- F. This is metastatic disease from of unknown cancer since she is on immunosuppression and this put her on increase risk of malignancy



# Case 3: pregnancy immunosuppression

- 25 yo F with LDKT in 2016 from her sister, on MMF and Tacrolimus was admitted to the hospital for bacterial pneumonia. She is ready to be discharge. While you are talking with her about discharger follow up, she tells you she plans to become pregnant. What do you think is the best advice for her:
- A. Is to soon after the transplant to be pregnant
- B. Please follow up with your transplant nephrologist to adjust your immunosuppression
- C. Explain that pregnancy will increase her risk for rejection
- D. Explain to her that Tacrolimus is associated with IUGR
- E. All of the above
- F. B,C and D



# Case 4: surgery and immunosuppression

- 78 yo M with PMH significant for LDKT 6 years ago, on Sirolimus, MMF 1 g BID and Prednisone 5 mg QD, came to the hospital with SBO. Initial conservative management failed, and the patient will need surgery. Which of the following you will consider to change in the immunosuppression of this patient:
- A. Stop Sirolimus, consider to switch to Tacrolimus based on his immunologic risk
- B. Switch MMF to AZA
- C. Give stress dose steroids during surgery
- D. Give stress dose steroids and give MMF iv
- E. A and D



# Case 5: medication interaction

- 57 yo F with past medical history for DMT2, COPD, ESRD status post DDKT in 2014, came to ED with seizure after she stopped taking her Phenytoin. She is on Tacrolimus 1 mg BID and MMF 750 mg BID. When you examine her you notice tremor of the hands. No graft tenderness. On her labs her Cr is 2. She tells you she stop taking her Phenytoin one week ago. She noticed lately some decrease in her urinary output. You order UA, US of the transplanted kidney. What do you do next:
- A. Send Tacrolimus level and call IR / nephrology consult for possible kidney Bx thinking this is rejection because the Tacrolimus level decreased after stopped taking her Phenytoin
- B. Send Tacrolimus level, call nephrology consult and hold his next Tacrolimus dose, thinking this is Tacrolimus toxicity
- C. Send MMF level, call IR/nephrology consult for possible kidney Bx thinking MMF level was to low after stopping Phenytoin and patient has an acute rejection
- D. Send MMF level, call nephrology consult and hold MMF, thinking that this is MMF toxicity



# Case 6: Side effects of immunosuppression

- 55 yo AA F with PMH of DDKT in 2013, on Tacrolimus 3 mg BID MMF 750 mg BID and Prednisone 5 mg QD was admitted with HCAP. During her hospitalization she has been having elevated glucose. FS 250 mg most of the time. A Hg A1c was checked, and is 9. Which of her medication makes diabetes worse.
- A. Prednisone
- B. MMF
- C. Tacrolimus
- D. A and B
- E. A and C



# Case 7: graft function

- 55 yo F school teacher, with a SKPT in 2014 on Tacrolimus, MMF and Prednisone came to the ED with diarrhea over the last 5 days. She was found with low BP of 90/60 mmHg, HR of 100 bit/min. On labs she has a Cr of 2 ( baseline one mo ago was 1) with BUN of 40 mg/dl. Her Na is 132 mg /dl, with bicarbonate of 20s. Stool studies found her with norovirus infection. She gets 2 L of NS. Her BP goes to 120s/70s. She feels much better. Her diarrhea persist. Next day you check her Cr. Is now 3. What do you do next:
- A. Give one dose of steroids, call IR to schedule a kidney Bx and call transplant / nephrology consult
- B. Send UA, Uc do an US of the kidney
- C. Check tacrolimus level
- D. Check MMF level
- E. B and C
- F. B and D



# Why is it important to know about transplant patients

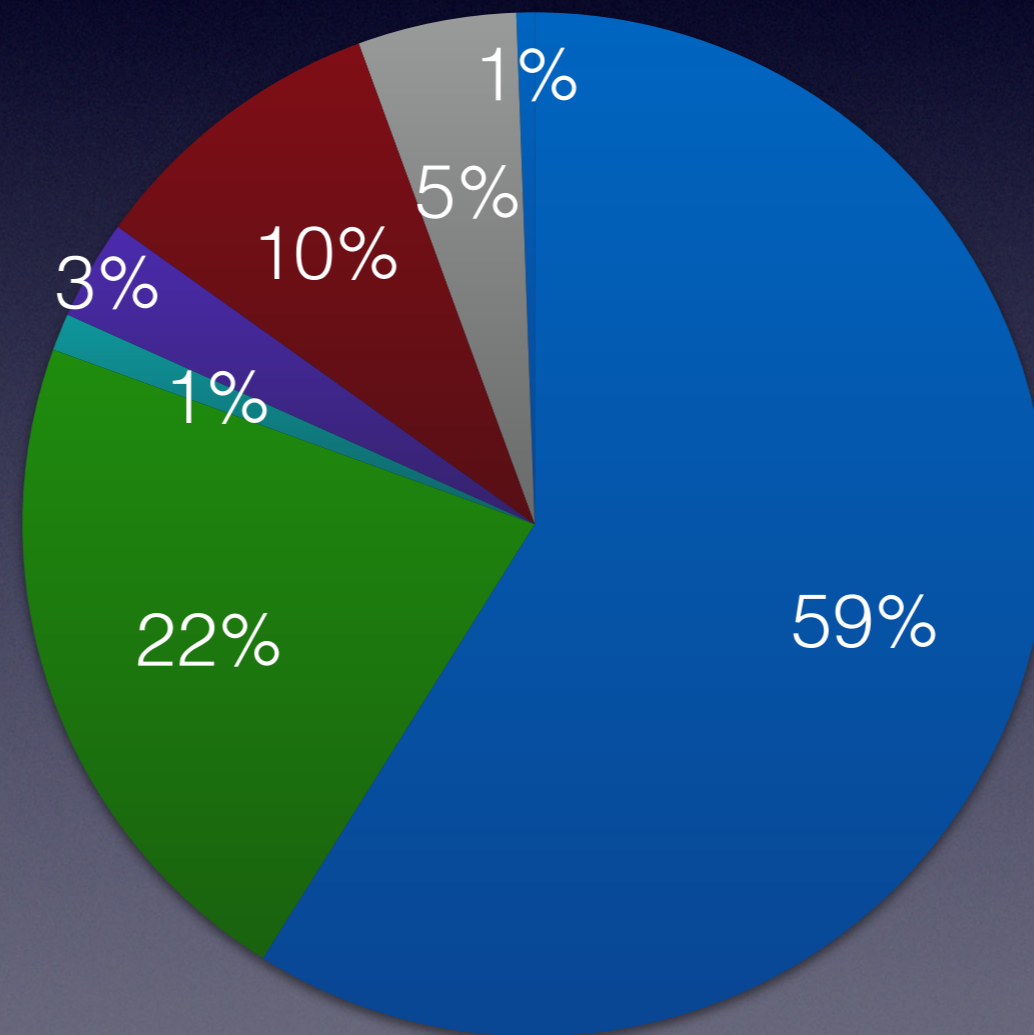
- 739,437 transplants since January 1988 <sup>1</sup>
- 17935 organ transplants were performed in 2018 <sup>2</sup>
- On average 95 transplants take place each day in US <sup>1</sup>
- 244 kidney transplant center in US
- 5534 registered hospitals in UA <sup>3</sup>

1.OPTN 2.UNOS. 3.AHA



# Transplants by organ type

## Jan 1988-July 2018





# Data from our hospital

- 47 transplanted patients in our hospital were admitted in 2018



# Question?

- Do we know what we don't know?



# Particularities of transplanted patient

- Graft ( transplanted organ) - function
- Chronic immunosuppression
- Complex patients with multiple comorbidities



# Graft/kidney -function

- Goal to keep the organ working as long as possible
- LD kidney last approximately 20 years
- DD kidney last approximately 10-12 years

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# Complex patient with multiple comorbidities

- Number one cause of ESRD is still T2DM
- Chronic immunosuppression more prone to infection and virus related malignancy



# Chronic immunosuppression

- Patient is on medication that comes with side effects that can be the cause of patient symptoms
- Predispose to infection, different forms of malignancy



# How do assess graft function

- What is the baseline Cr ?
- What is the maintenance immunosuppression regiment ?
- When was the last time when the patient took immunosuppression medication ?



# Cr elevated

- Is this a rejection ?



# Is this rejection?

- What is the risk of rejection ?
- Was the immunosuppression compromised by admission disease ?



# What is the risk of rejection for this patient

- **How long ago was the transplant ?**
- **Other important factors:** age of transplant, patient race , type of transplant , prior transplant, prior rejection
- **High risk:** 18-60 yo, Black, DD, previous transplant, combined transplant ( except liver), previous rejection, late rejection after transplant
- **Other risk factor** (unlikely to get them from the patient): HLA A,B, DR>1 mismatch
- Type of transplant: intestine>lung>heart>pancreas> kidney>liver



# Was the immunosuppression compromised by admission disease

- Recent change in medication that can interfere with metabolism of immunosuppression
- Inability to take their medication: nausea, vomiting, SBO.
- Pregnancy



# Immunosuppression

- What regiment it patient on ?
- Has he/she been taking her medication?
- When was the last dose?



# Immunosuppression

- Immunosuppression medications by class
- Current most used maintenance immunosuppression therapy for kidney transplant
- Medication interaction
- Medication side effects
- Immunosuppression / graft function/ admission diagnosis interrelation



# Immunosuppression medication by class

CNI

Tacrolimus and Cyclosporine

mTOR

Sirolimus and Everolimus

Steroids

Prednisone

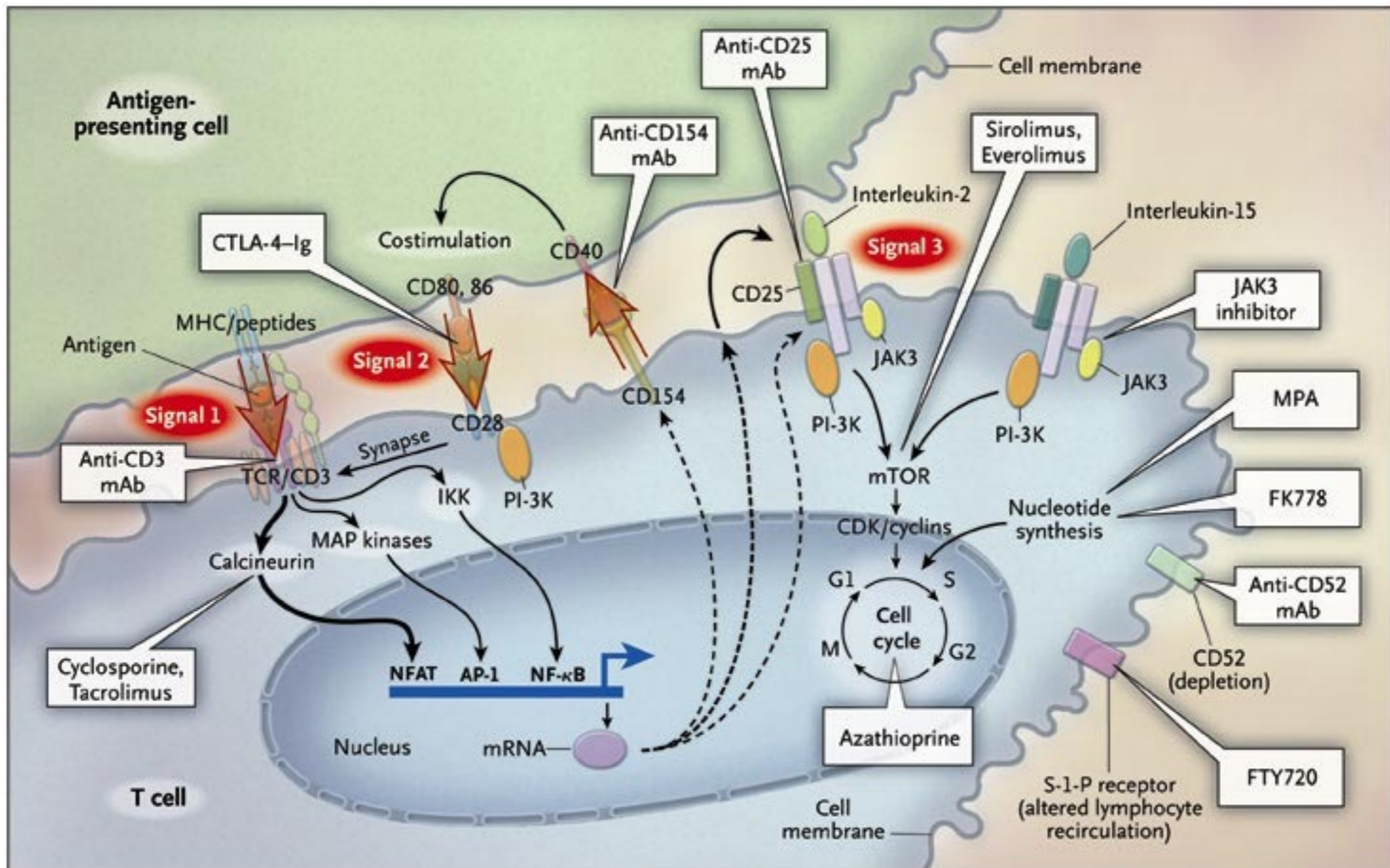
Antimetabolite

MMF and AZA

Belatacept



# How do they work





# Chronic immunosuppression protocols 2018

- Main protocol: MMF, CNI with or without Prednisone 0.1 mg /kg/day
- Other protocols: combination of antimetabolite with MTOR , Bellatacept, Prednisone and antimetabolite.



# Medication side effect by class



# Tacrolimus vs cyclosporine

- Nephrotoxicity
- Hypertension (CSA > Tacro)
- Post-transplant DM ( Tacrolimus > CSA)
- Neurological ( Tacrolimus)
- Hirsutism ( CSA) / Alopecia ( Tacrolimus)
- HLD ( CSA > Tacrolimus)



# Sirolimus vs Everolimus

- Acne/rash
- Mouth ulcers
- HLD
- anemia/thrombocytopenia
- Proteinuria ( rare) : Bx: FSGS, podocyte injury
- Pneumonitis ( 4-11%) Sirolimus > Everolimus
- Sirolimus: anemia, NODAT



# Belatacept

- EBV seronegative recipients have a 9 th fold increased risk of CNS PTLD .
- EBV sero-positive recipients treated with Belatacept still have an increase risk of PTLD compared with patients treated with Cyclosporine



# MMF vs Azothioprine

- Bone marrow toxicity (AZA >MMF)
- MMF birth defect
- MMF dose related nausea, gastritis and diarrhea



# Prednisone

- HTN
- DM
- Aseptic necrosis of the femoral head, osteoporosis.
- Other side effects: GI, skin, muscle, fracture



# Medication interaction with common used drugs



# Important CNI medication interaction

- Drug that increase CNI level
- Drug that decrease CNI level
- Other medication interaction



# Drugs that increase CNI level

- Ca channel blockers : Diltiazem, Verapamil, Amlodipine, Nicardipine (40% dose reduction)
- Antifungal agents: Ketoconazole, Fluconazole, Itraconazole, Voriconazole (80% dose reduction ).
- Antibiotics: Macrolide (Clarithromycin), Chloramphenicol (Tacrolimus), Erythromycin
- mTOR: increase CNI level



# Drugs that decreased CNI level

- Antituberculosis drugs: Rifampin, Rifabutin, Isoniazid
- Anticonvulsant: Barbiturates, Phenytoin, Carbamazepine
- Herbal preparation: St. John's wort
- Cholestiramine ( decreased absorption)



# Exaggerate side effects of other medications

- Rhabdomyolysis: Lovastatin used with CSA ( 6 weeks to 16 mo after starting the therapy) . Recommended dose is 20 mg.
- Nephrotoxicity: Amphotericin, NSAID, ACE,ARB
- Hepatotoxicity: Ranitidine and CSA



# Elevated Cr

- Look for nephrotoxicity from CNI. Check 12 hours levels for Tacrolimus and CSP
- Look for drug interaction and inquire regarding change in medication
- Look for caused of change in drug levels :  
diarrhea increased tacrolimus level



# Admission diagnosis interrelation with chronic immunosuppression

- Infection
- Malignancy
- Cardiovascular
- Diabetes
- Surgery

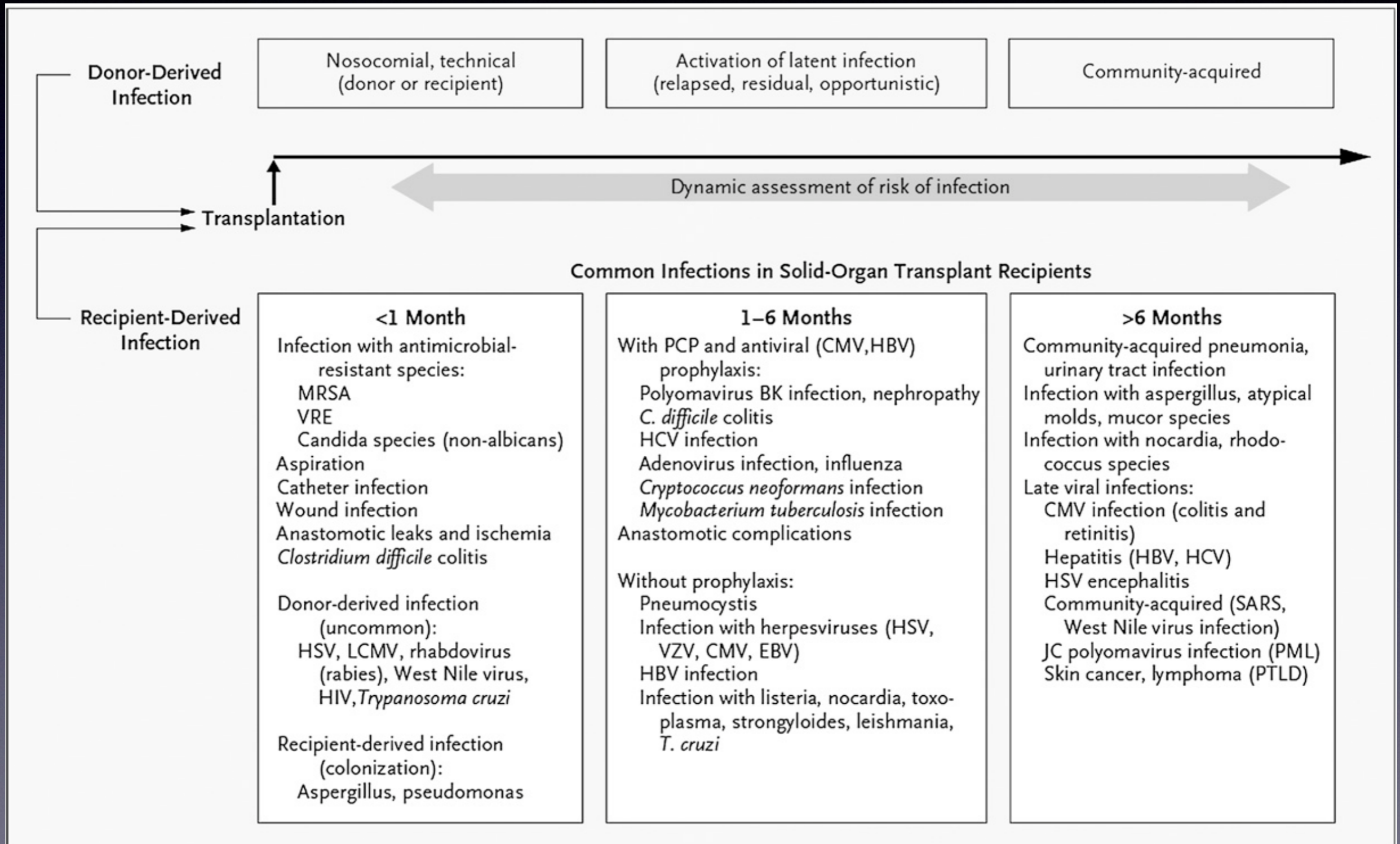


# Concepts in transplant patients with infection

- Patient is on chronic immunosuppression
- Screen for atypical infection: CMV , EBV, BK
- If you patient is septic : hold MMF, consider stress dose of steroids if you patient has been on Prednisone form more then 6 mo
- Consider longer treatment for infection, ID consult
- If recurrent infection contact the transplant center with regard to reduction in immunosuppression.



# Common infection





# BKV

- Polyomavirus present in the urinary tract
- Can cause nephropathy or urinary tract stenosis
- Dx: elevated Cr and BKVL >10.000. Kidney Bx
- **Treatment :**
- Prevention: BK screening mo for first 3 mo, then every mo until one year
- BK VL >10.000 copies, reduce immunosuppression
- Bx proven BK nephropathy: Tacrolimus level <6, switch MMF to Lefunomide



# CMV

- CMV disease: clinical signs and symptoms and CMV VL present in plasma
- Manifested: viral illness with leucopenia and lymphocytosis or tissue invasion ( Pneumonitis, diarrhea)
- **Treatment:**
- Prophylactic: treatment with Valgancyclovir or Gancyclovir 3-6 mo after transplant. Exception CMV Donor neg /Rec. neg
- CMV disease: tissue invasion -iv Gancyclovir, non-invasive -iv Gancyclovir or po Valancyclovir , until CMV by NAT is negative.
- CMV VL by NAT will be checked weekly



# EBV

- High risk recipients: EBV negative with donor EBV positive
- High risk recipients: monitor EBV VL every mo 3-6 mo, then every 3 mo until one year.
- **Treatment:**
- EBV VL increase, reduce immunosuppression



# Malignancy risk

## **Increased incidence of cancer**

Much higher  
Skin  
Kaposi's.  
Vulvovaginal  
Lymphoma  
Kidney

Higher  
Uterine cervix  
Liver

## **Not different**

Breast  
Prostate  
Testicular  
Ovarian  
Lung  
Colon



# Recurrent Skin cancer

- Skin cancer incidence in transplant patients: SCC 100 % increased risk, BCC and melanoma
- Risk factors: age at transplantation >55 yo, duration of immunosuppression (40-60% by 20 years), organ transplanted ( heart, kidney, liver)
- **Treatment:**
  - *Non-melanoma*
    1. Call transplant center since you patient can benefit from reduction in immunosuppression change in immunosuppression like switch form CNI to mTOR<sup>1</sup>
    2. Use Acitretine topical <sup>2</sup>
    3. Nicotinamide 500 mg BID <sup>3</sup>
  - *Melanoma:* call your friend oncologist

1.Stallone G, NEJM 2005;352-1317  
2.KIDIGO 2009



# PTLD

- Lymphoma occurring post-transplant related to immunosuppression
- EBV mediated (80%), or not mediated
- Most within 2 years post-transplant
- Increase risk with high immunosuppression
- Lesions within transplanted organs are common
- Treatment: Lower immunosuppression, Rituximab and Chemotherapy



# Cardio vascular

- Number one cause of death with a functional graft
- Transplanted patients have an increase risk of cardiac death compared with general population
- Some of immunosuppression medication cause: HLD, DM
- **Treatment:**
- Consider managing at list as intensive as in general population <sup>1</sup>
- ACE and ARB have been associated with post-transplant anemia
- HLD:mTOR, more with CSA > Tacrolimus
- mTOR could be anti-atherogenic
- Precaution with CNI and Lovastatine



# Diabetes

- NODAT / diabetes at the time of transplant
- Risk factors for NODAT : mTOR, Tacrolimus > CSA .
- NODAT increase risk of cardiovascular events
- **Treatment:**
- ASA 81 mg if DM /NODAT and age >40 yo, smoking, HLD,HTN, family history of CV disease
- Glycemic control: Hg A1c 7-7.5
- Consider modifying immunosuppression therapy to reverse or ameliorate diabetes, after weighting the risk of rejection and other potential adverse effect



# Surgery

- Switch immunosuppression to iv
- Switch mTOR to CSA or Tacrolimus



Transplanted organ function



Maintenance immunosuppression



Diagnosis of admission



# Safe discharge

- Call transplant coordinator and inform her about the patient hospitalization and any new medication
- Have follow up on immunosuppression drug levels after hospital admission, if during the hospitalization there was any change in the patient medication or the drug levels were not at goal.



# Conclusions

- Transplant patient is complex
- Immunosuppression medication plays an important role in some of the common diseases requiring hospitalization
- The goal is to keep the patient alive and keep the graft functioning



Thank you !

