Inpatient Management of Solid Organ Transplant Patients

2022 ACP Washington Chapter Annual Meeting – Inpatient Precourse

November 3, 2022

Yilin Zhang, MD[1]

Jesse A. Levin, MD[2]

[1]Clinical Assistant Professor, University of Washington, Department of Medicine, Division of General Internal Medicine, Valley Medical Center

[2]Clinical Assistant Professor, University of Washington, Department of Medicine, Division of General Internal Medicine, UWMC-Montlake

Disclosures

- We have no disclosures

Goals

Train Transplant Medicine Specialists

Increase comfort with initial *inpatient* evaluation of patients with solid organ transplant (SOT)

Always have a low threshold to call the Transplant Center early!

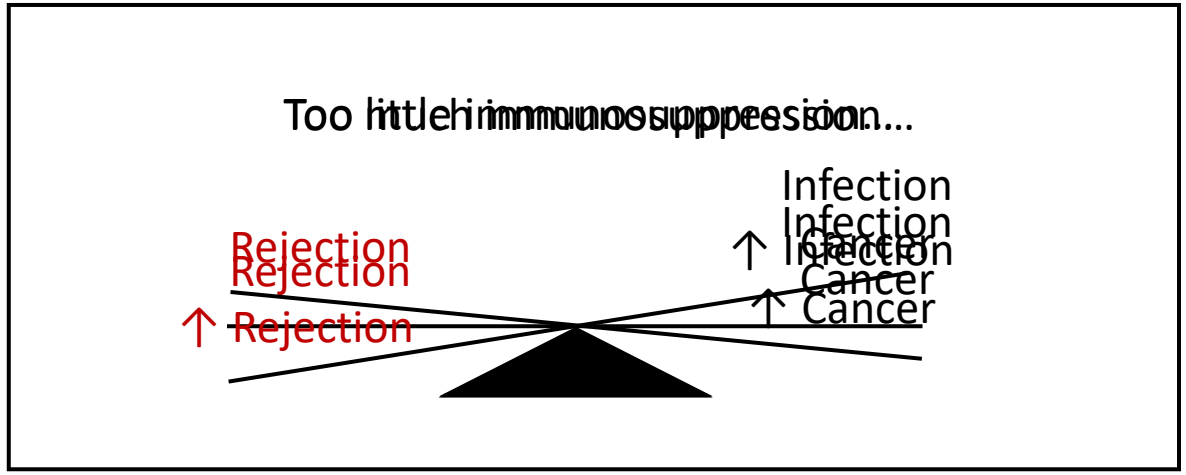
Objectives

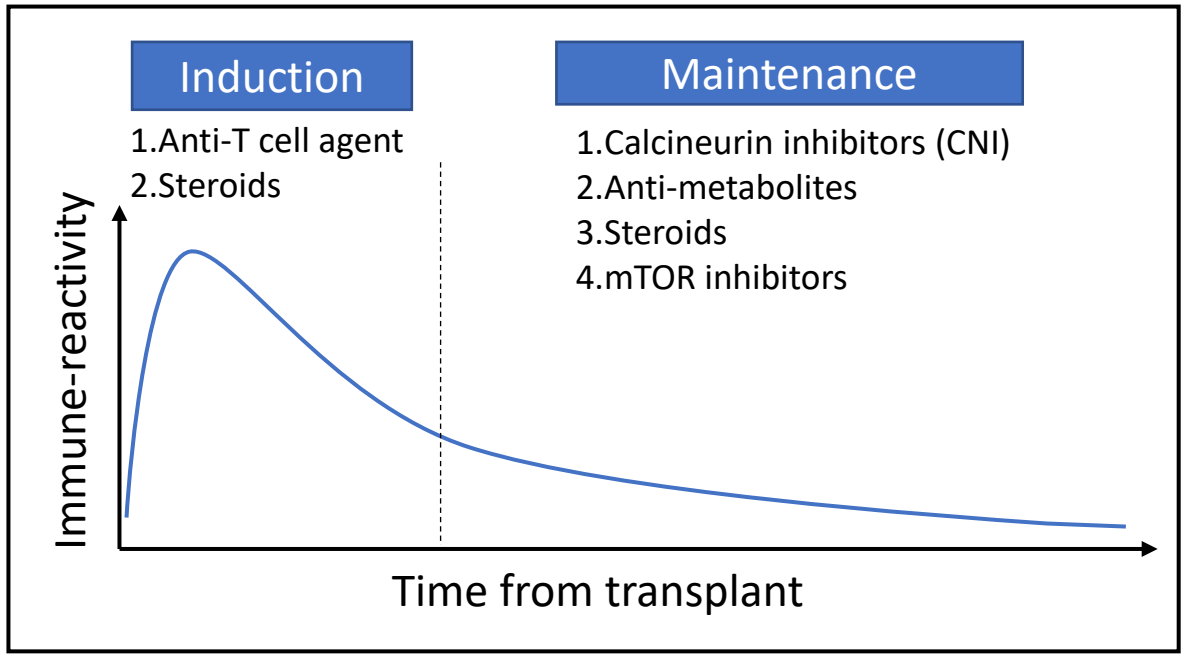
By the end of this talk, you will be able to…

1. Develop a framework for understanding common complications after SOT, related to timing after transplant
2. Initiate a basic evaluation for patients presenting with organ dysfunction
3. Identify common transplant medication side effects and drug interactions

Transplant Basics

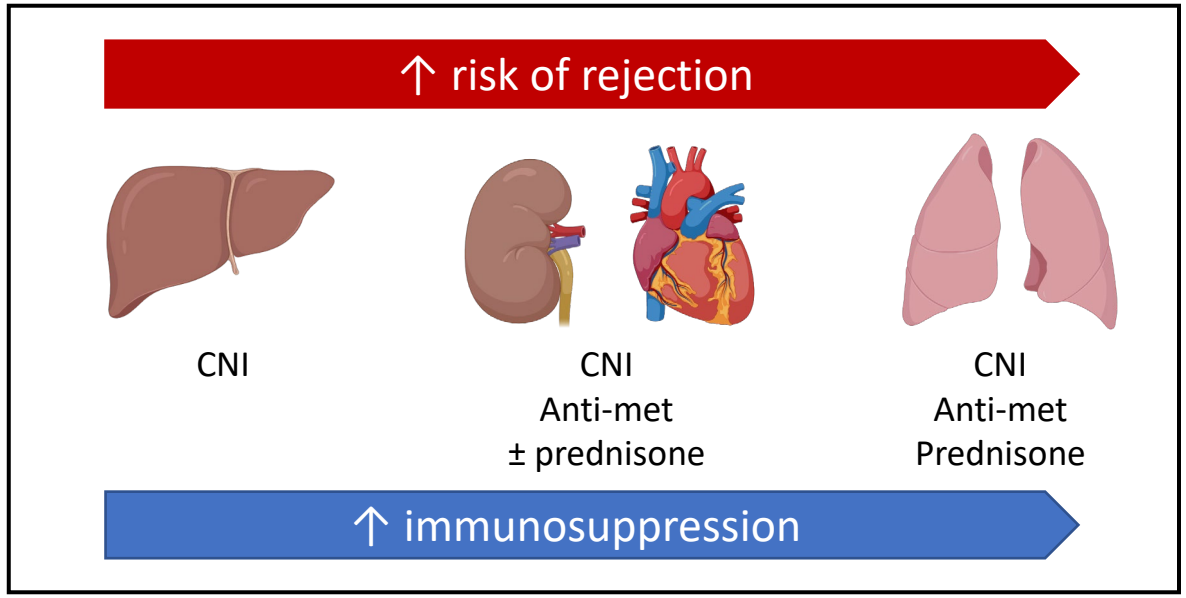
- Core principle of Transplant Medicine is balancing immunosuppression
- The amount of immunosuppression depends on:
  - Time from transplant

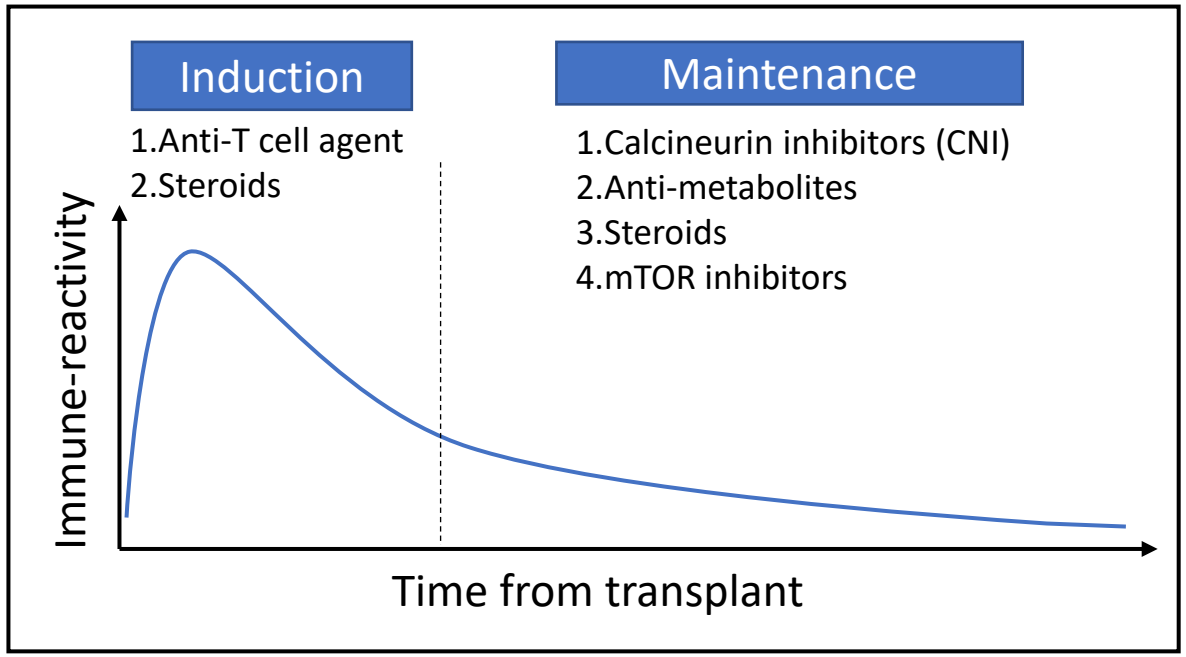




Transplant Basics

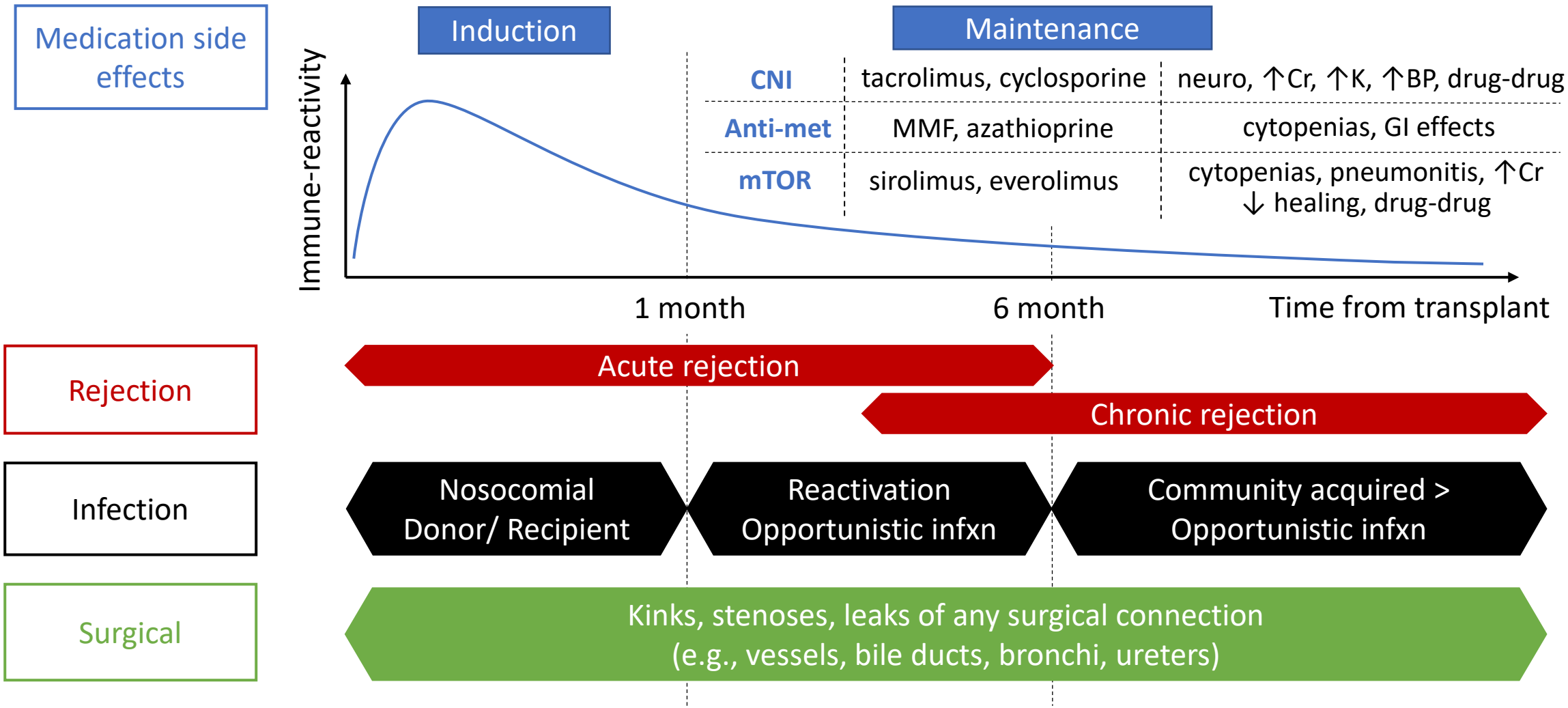
- Core principle of Transplant Medicine is balancing immunosuppression
- The amount of immunosuppression depends on:
  - Time from transplant
  - Organ transplanted
  - Complications of immunosuppression





Images created with Biorender.com

Complications



Case 1

63 yo with a history of alcohol-related cirrhosis s/p liver transplant 5 years ago

Case 1

63 yo with a history of alcohol-related cirrhosis s/p liver transplant (5 y ago, CMV D+/R-) who presents with 4 d of malaise, abdominal pain, nausea/vomiting. Denies sick contacts. Denies alcohol use.

Medications

Cyclosporine

Exam

T 37.9C, HR 113, BP 110/56
RR 22, SaO_2 97% on RA
Lungs: Clear to auscultation.
CV: Tachycardic, no murmurs
Abdomen: RUQ chevron scar.
Skin: Jaundiced.

Labs

143	112	25	125
3.9	22	1.1	

13.5	9.9 / 135 / 31

AST 232 Tbili 4.3
ALT 350 ALP 232

INR 1.4

COVID PCR: negative

What are your next steps in evaluation?

A. Serum and drug tox screen
B. Acute hepatitis panel
C. RUQ ultrasound
D. Liver ultrasound with duplex
E. Verify medication history
F. Cyclosporine trough
G. CMV PCR

What are your next steps in evaluation?

<Poll #1 Responses>

What are your next steps in evaluation?

A. **Serum and drug tox screen**
B. **Acute hepatitis panel**
C. **RUQ ultrasound**
D. **Liver ultrasound with duplex**
E. **Verify medication history**
F. **Cyclosporine trough**
G. **CMV PCR**

What are your next steps in evaluation?

A. Serum and drug tox screen

B. Acute hepatitis panel

C. RUQ ultrasound

D. Liver ultrasound with duplex

E. Verify medication history

F. Cyclosporine trough

G. CMV PCR

Evaluation of graft dysfunction should include typical evaluation for native organ dysfunction.

e.g., acute liver injury in liver transplant, AKI in renal transplant, hypoxia in lung transplant, reduced LVEF in heart transplant

What are your next steps in evaluation?

A. Serum and drug tox screen

B. Acute hepatitis panel

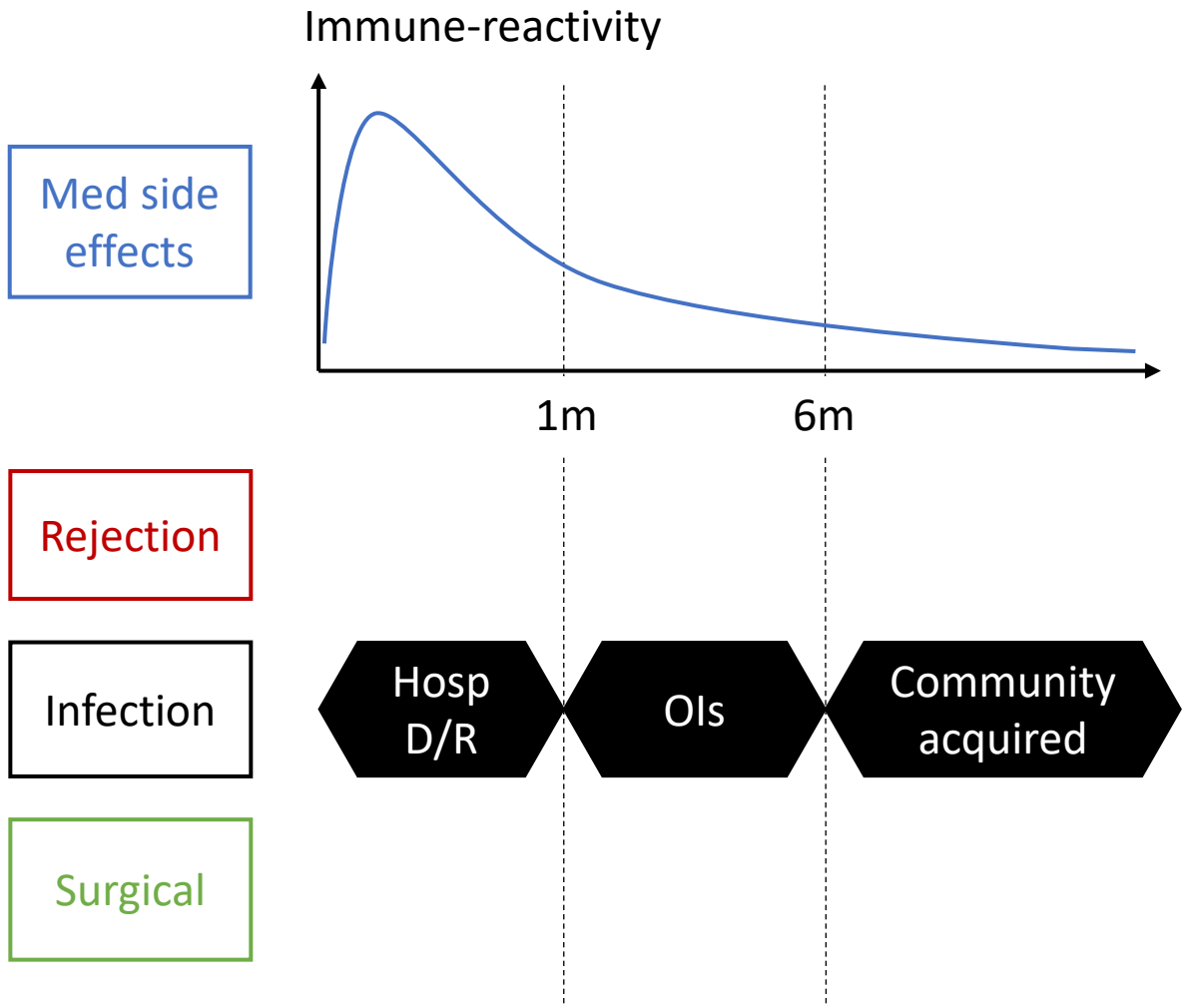
C. RUQ ultrasound

D. Liver ultrasound with duplex

E. Verify medication history

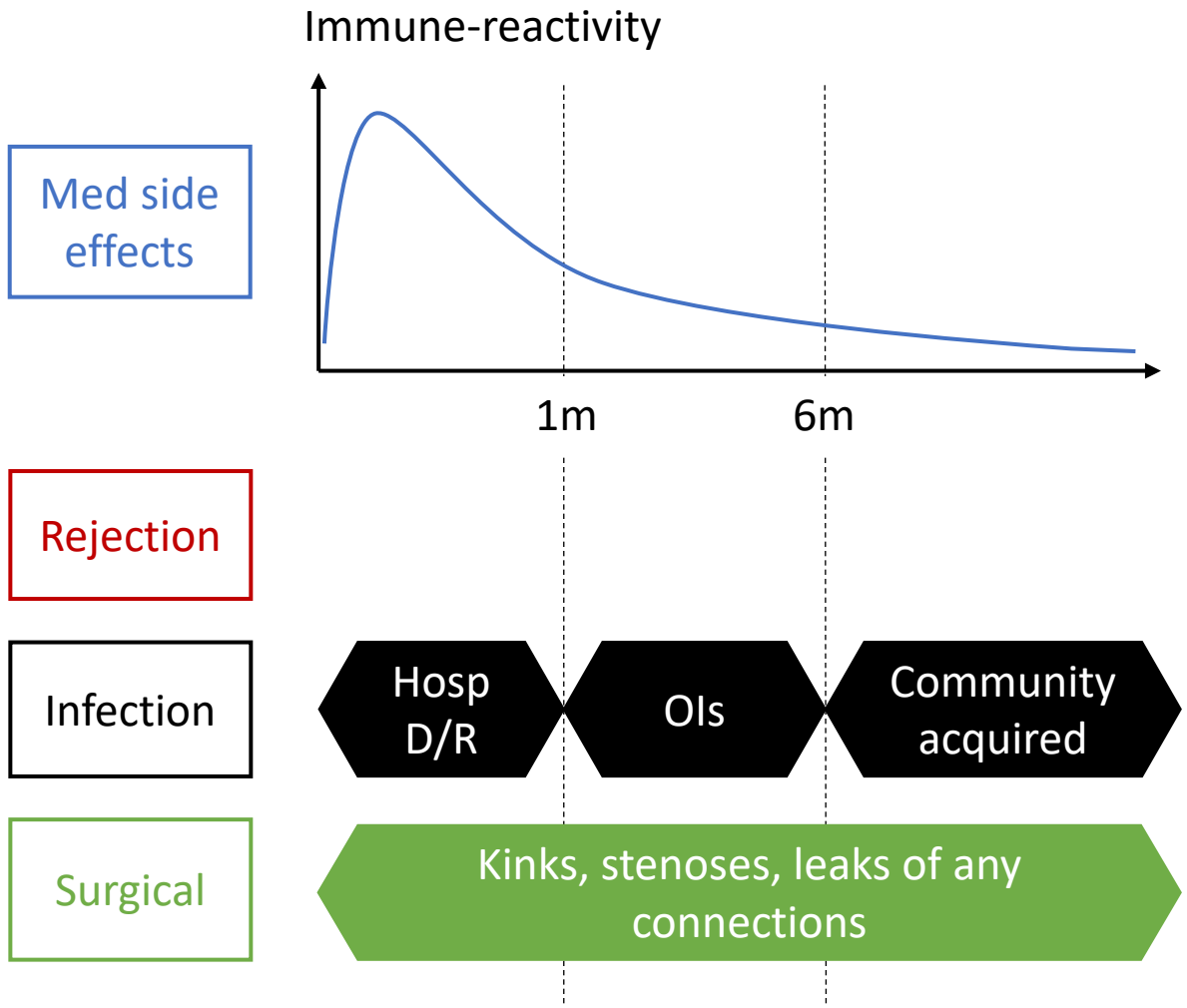
F. Cyclosporine trough

G. CMV PCR



What are your next steps in evaluation?

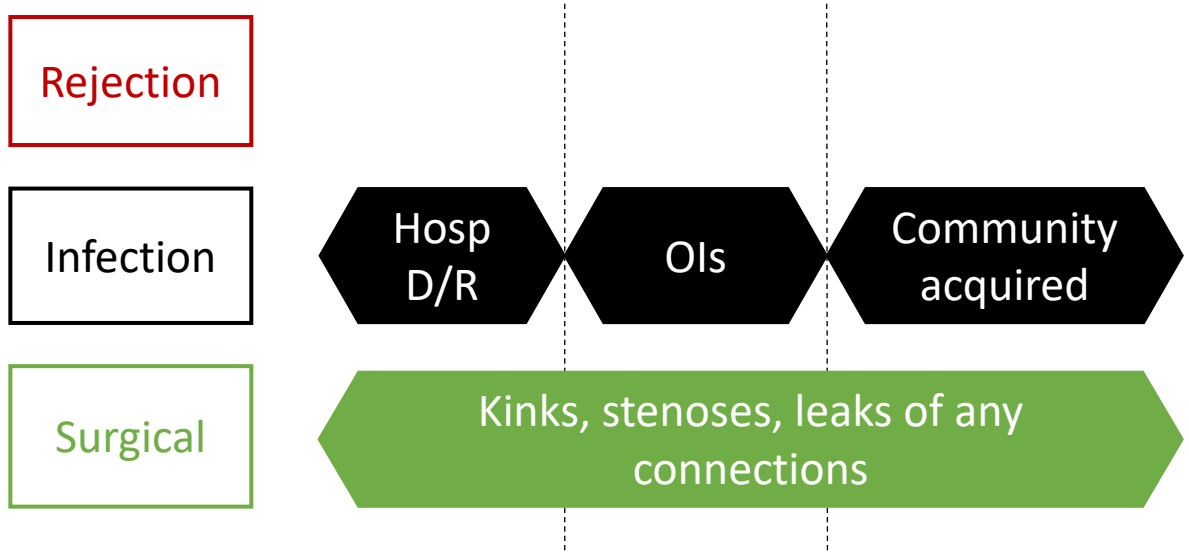
A. Serum and drug tox screen
B. Acute hepatitis panel
C. RUQ ultrasound
D. Liver ultrasound with duplex
E. Verify medication history
F. Cyclosporine trough
G. CMV PCR



What are your next steps in evaluation?

A. Serum and drug tox screen
B. Acute hepatitis panel
C. RUQ ultrasound
D. Liver ultrasound with duplex
E. Verify medication history
F. Cyclosporine trough
G. CMV PCR

Evaluate for post-surgical complication (vascular stenoses) using duplex in patients presenting with graft dysfunction.

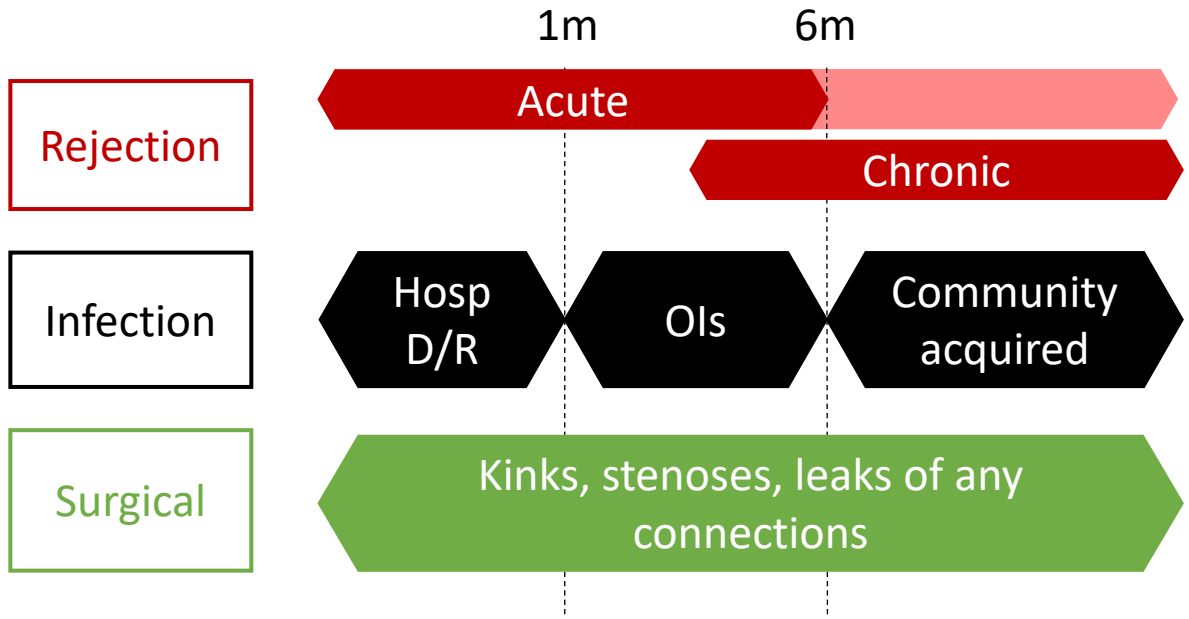


What are your next steps in evaluation?

A. Serum and drug tox screen
B. Acute hepatitis panel
C. RUQ ultrasound
D. Liver ultrasound with duplex
E. Verify medication history
F. Cyclosporine trough
G. CMV PCR

Consider rejection in patients with graft dysfunction.

Acute rejection is most common <6 mos. Later, it occurs with under-immunosuppression.

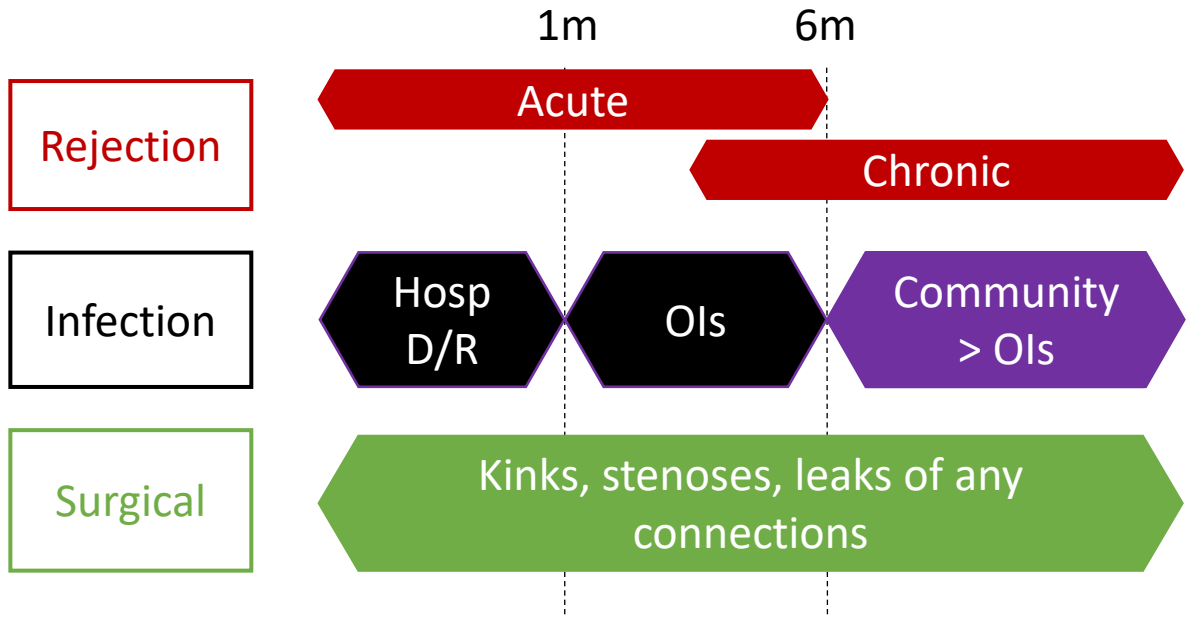


What are your next steps in evaluation?

A. Serum and drug tox screen
B. Acute hepatitis panel
C. RUQ ultrasound
D. Liver ultrasound with duplex
E. Verify medication history
F. Cyclosporine trough
G. CMV PCR

Consider CMV status in patients!

There is still risk for OIs in the late post-transplant period with ↑ immunosuppression.



Case 1

63 yo with a history of alcohol-related cirrhosis s/p liver transplant (5 y ago, CMV D+/R-) who presents with 4 d of malaise, abdominal pain, nausea/vomiting. Found to have acute liver injury.

Medication reconciliation showed no fills on cyclosporine for 4 months. Cyclosporine trough came back undetectable.

They were diagnosed with acute cellular rejection and started on re-induction immunosuppression.

Case 2

55 yo with history of ILD who underwent a bilateral orthotopic lung transplant (BOLT) 3 months ago

Case 2

55 yo with history of ILD s/p BOLT (3 mos ago, CMV D+/R+) presents with increased SOB and productive cough x 3 d. Sputum is thick, white. No fevers, chills, URI symptoms, chest pain, or sick contacts.

Medications

Prednisone
MMF
Tacrolimus
TMP/SMX
Valganciclovir

Exam

T 37C, HR 113, BP 110/56
RR 28, SaO_2 87% on RA
Lungs: ↑WOB, diffuse crackles, no wheezing
CV: Tachycardic, no JVD or LE edema

Labs

143	112	25	125
4.9	22	1.1	

	9.9	
3.5		135
	31	

BNP 87
Trop negative
COVID PCR: negative
CXR: diffuse patchy bilateral infiltrates

What are your next steps in evaluation?

A. Send extended viral PCR
B. Send sputum culture, urinary Legionella and Strep Ag
C. Consult Pulmonology to consider bronchoscopy
D. Send serum CMV PCR
E. CT chest

What are your next steps in evaluation?

<Poll #2 Responses>

What are your next steps in evaluation?

A. **Send extended viral PCR**
B. **Send sputum culture, urinary Legionella and Strep Ag**
C. **Consult Pulmonology to consider bronchoscopy**
D. **Send serum CMV PCR**
E. **CT chest**

What are your next steps in evaluation?

A. **Send extended viral PCR**
B. **Send sputum culture, urinary Legionella and Strep Ag**
C. Consult Pulmonology to consider bronchoscopy
D. **Send serum CMV PCR**
E. CT chest

Exam
T 37C, HR 113, BP 110/56 RR 28, SaO_2 87% on RA

Labs
9.9 3.5 135 31

What are your next steps in evaluation?

A. **Send extended viral PCR**
B. **Send sputum culture, urinary Legionella and Strep Ag**
C. Consult Pulmonology to consider bronchoscopy
D. **Send serum CMV PCR**
E. CT chest

Maintain a high suspicion for infection. Immunosuppression may blunt fever or leukocytosis.

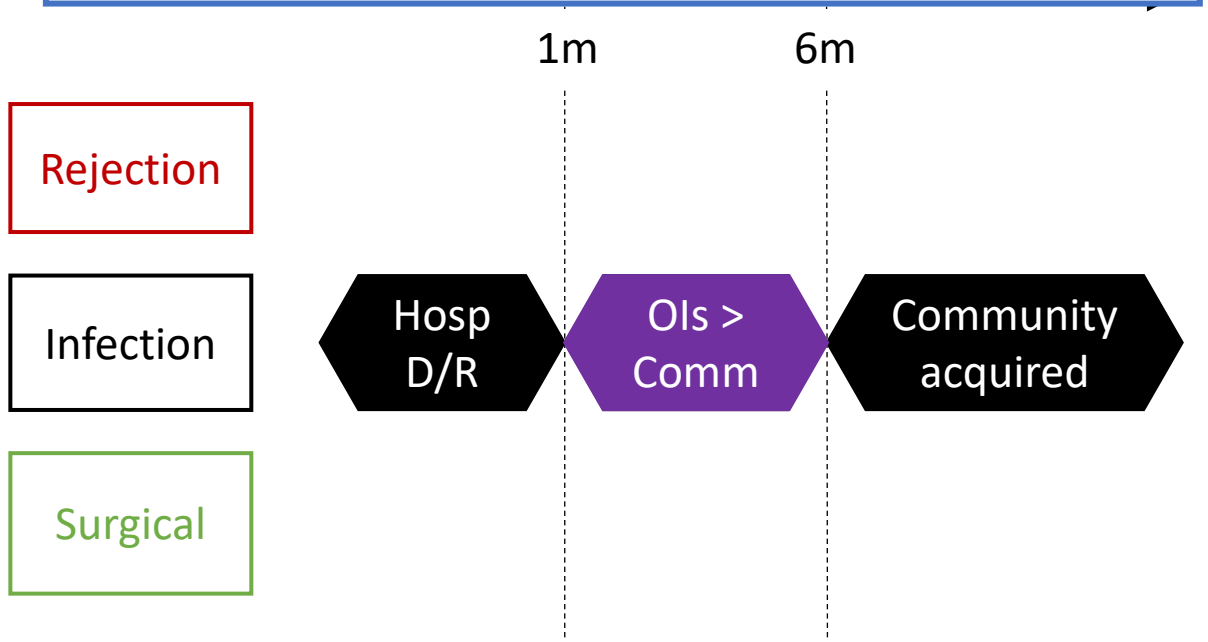
Exam
T 37C, HR 113, BP 110/56 RR 28, SaO_2 87% on RA

Labs
9.9 3.5 135 31

What are your next steps in evaluation?

A. **Send extended viral PCR**
B. **Send sputum culture, urinary Legionella and Strep Ag**
C. Consult Pulmonology to consider bronchoscopy
D. **Send serum CMV PCR**
E. CT chest

Evaluation of graft dysfunction should include typical evaluation for organ dysfunction.



What are your next steps in evaluation?

A. **Send extended viral PCR**

B. **Send sputum culture, urinary Legionella and Strep Ag**

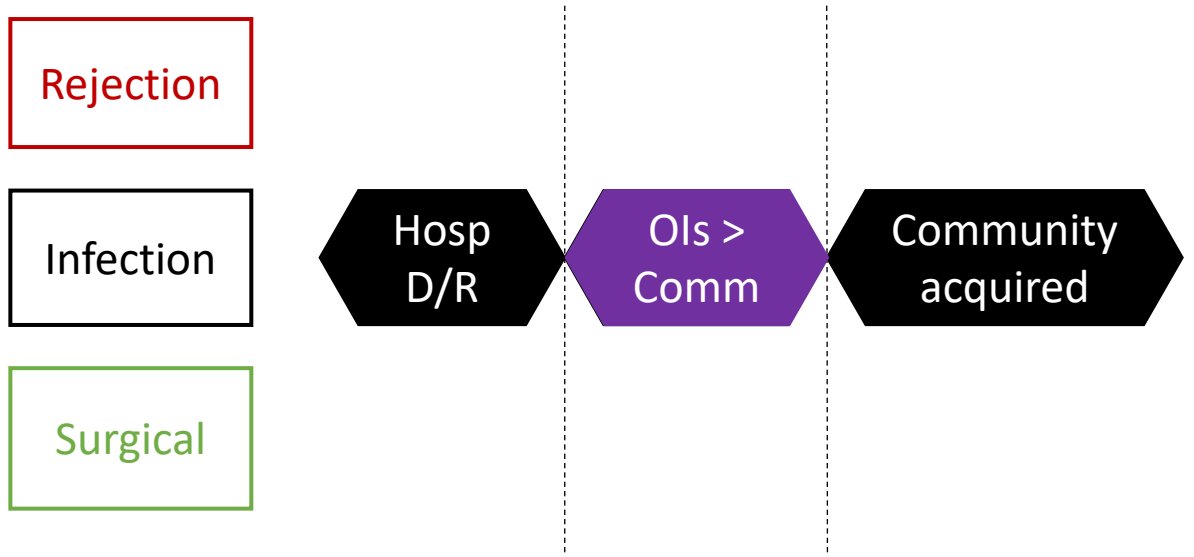
C. Consult Pulmonology to consider bronchoscopy

D. **Send serum CMV PCR**

E. CT chest

Viral infections are common and can cause significant morbidity after lung transplant.

Have a low threshold to check for respiratory viruses beyond flu and COVID.



What are your next steps in evaluation?

A. **Send extended viral PCR**

B. **Send sputum culture, urinary Legionella and Strep Ag**

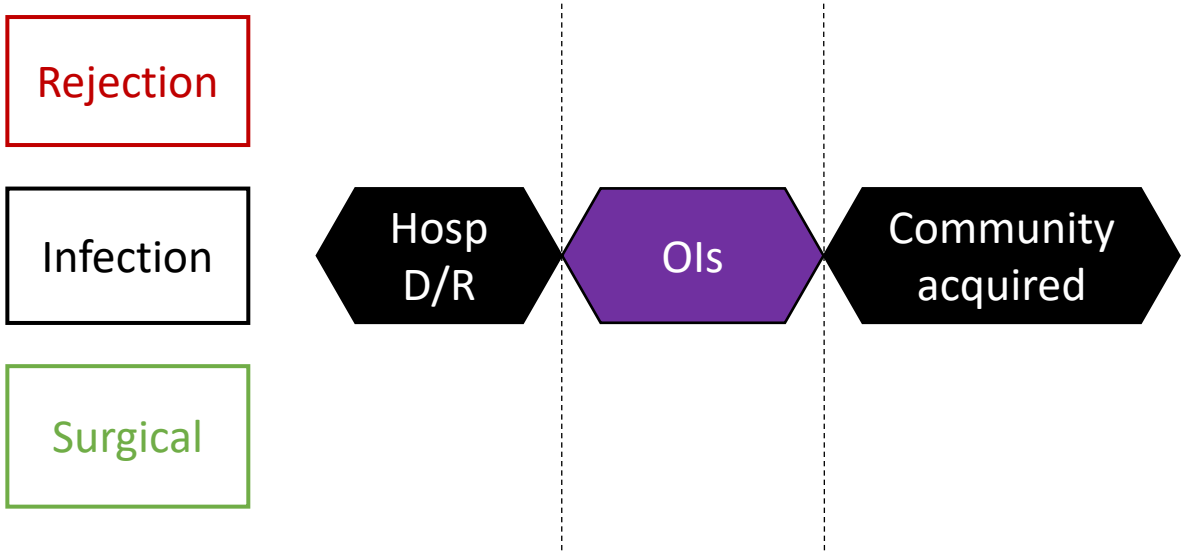
C. Consult Pulmonology to consider bronchoscopy

D. **Send serum CMV PCR**

E. CT chest

Note donor and recipient CMV status! CMV can reactivate and cause multiorgan damage.

CMV D+/R- are highest risk of CMV reactivation.



What are your next steps in evaluation?

A. Send for extended viral PCR, sputum culture

B. Consult Pulmonology to consider bronchoscopy

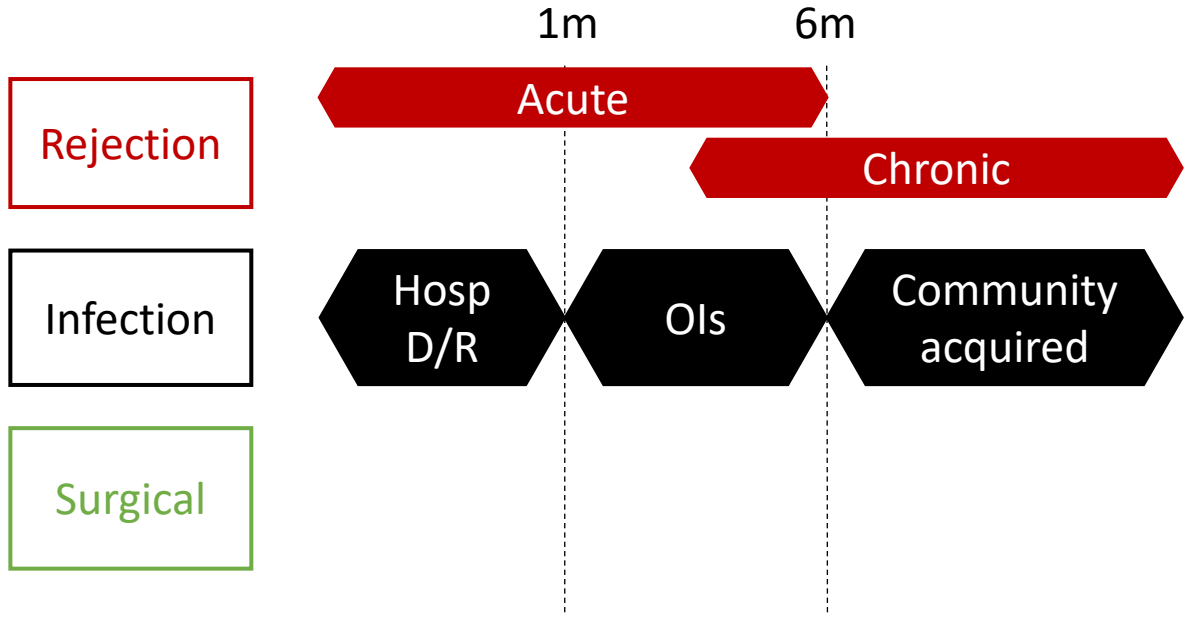
C. Send for CMV PCR

D. CT chest

The Transplant Team will help guide additional evaluation of rejection (biopsy, donor specific antibodies)

Consult Pulmonology early!

Bronchoscopy ***may*** be needed to differentiate between rejection and infection but is not needed for all patients.

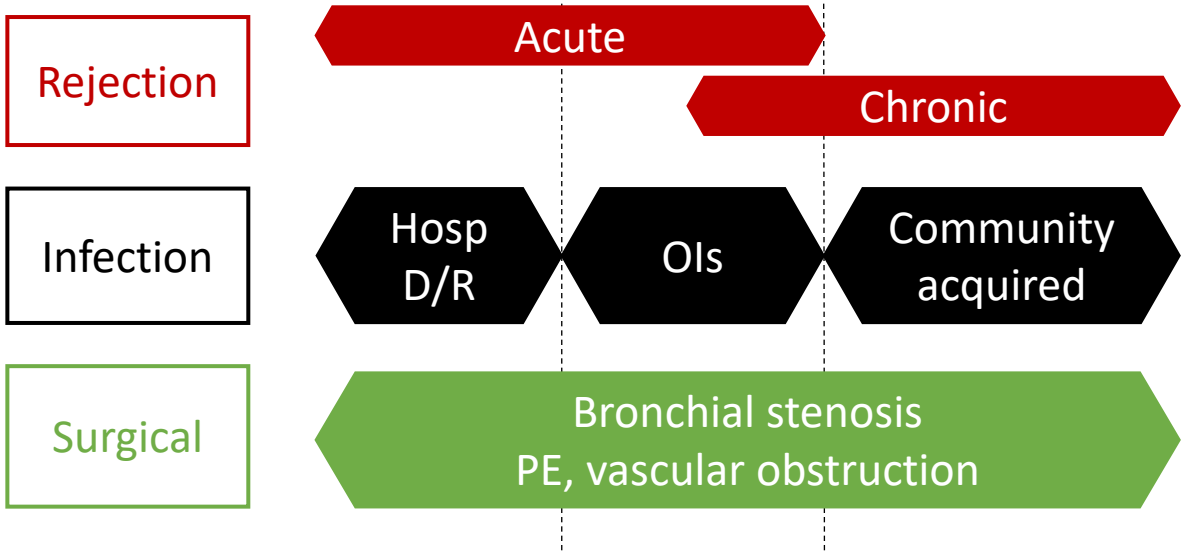


What are your next steps in evaluation?

A. Send for extended viral PCR, sputum culture
B. Consult Pulmonology to consider bronchoscopy
C. Send for CMV PCR
D. CT chest – can be considered

CT imaging (± angiography) ***may*** be helpful in differentiating causes of hypoxemia.

Many diagnoses, such as rejection, have nonspecific imaging findings.

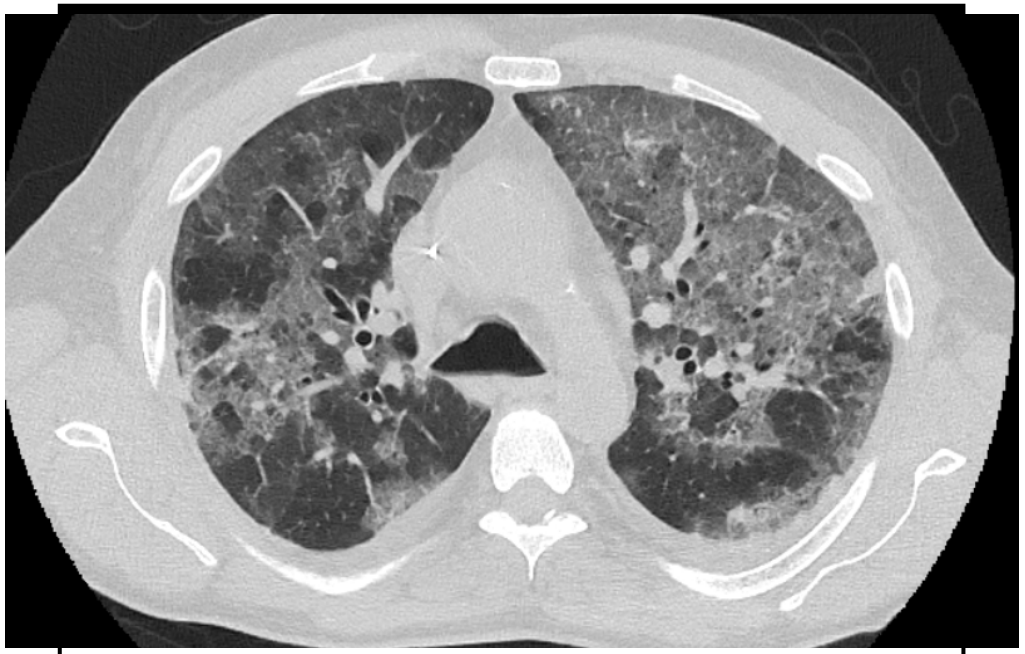


Case 2 cont…

55 yo with history of ILD s/p BOLT (3 mos ago, CMV D+/R+) presents with increased SOB and productive cough x 3 d. COVID negative. Blood and sputum cultures, MRSA nares, and viral PCRs pending.

They are placed on 2L NC with improvement in SaO2 to 94%.

CT chest showed no signs of bronchial stenosis and bilateral patchy GGOs, concerning for infection, inflammation, or edema.



Case courtesy of Dr Mostafa El-Feky, Radiopaedia.org, rID: 75400

Case courtesy of Dr Mostafa El-Feky, Radiopaedia.org, rID: 75400

What is your next step in management?

A. Hold immunosuppression. There is concern for pneumonia.
B. Give 30 cc/kg IVF for sepsis from possible pneumonia.
C. Give IV methylprednisolone 125 mg for possible ILD flare.
D. Start vancomycin + cefepime + azithromycin.

MOC

What is your next step in management?

<Poll #3 Responses>

What is your next step in management?

A. Hold immunosuppression. There is concern for pneumonia.
B. Give 30 cc/kg IVF for sepsis from possible pneumonia.
C. Give IV methylprednisolone 125 mg for possible ILD flare.
D. Start vancomycin + cefepime + azithromycin.

MOC

What is your next step in management?

~~A. Hold immunosuppression. There is concern for pneumonia.~~

B. Give 30 cc/kg IVF for sepsis from possible pneumonia.

C. Give IV methylprednisolone 125 mg for possible ILD flare.

D. Start vancomycin + cefepime + azithromycin.

Do NOT routinely hold immunosuppression in transplant patients with suspected infection.

What is your next step in management?

~~A. Hold immunosuppression. There is concern for pneumonia.~~

B. Give 30 cc/kg IVF for sepsis from possible pneumonia.

~~C. Give IV methylprednisolone 125 mg for possible ILD flare.~~

D. Start vancomycin + cefepime + azithromycin.

Do NOT routinely give corticosteroids without discussing with the Transplant Team.

Respiratory decompensation after BOLT is much more likely related to post-transplant complications than a patient's prior lung disease.

MOC

What is your next step in management?

~~A. Hold immunosuppression. There is concern for pneumonia.~~

~~B. Give 30 cc/kg IVF for sepsis from possible pneumonia.~~

~~C. Give IV methylprednisolone 125 mg for possible ILD flare.~~

D. Start vancomycin + cefepime + azithromycin.

Lung transplant patients are prone to pulmonary edema!
Manage volume judiciously.

Lymphatics are not connected with transplant. Err on side of withholding fluids if no hypotension or lactic acidosis.

MOC

What is your next step in management?

~~A. Hold immunosuppression. There is concern for pneumonia.~~

~~B. Give 30 cc/kg IVF for sepsis from possible pneumonia.~~

~~C. Give IV methylprednisolone 125 mg for possible ILD flare.~~

D. Start vancomycin + cefepime + azithromycin.

Cover broadly for nosocomial infections in the early post-transplant period.

Narrow based on culture results (e.g., stop vancomycin if MRSA nares negative).

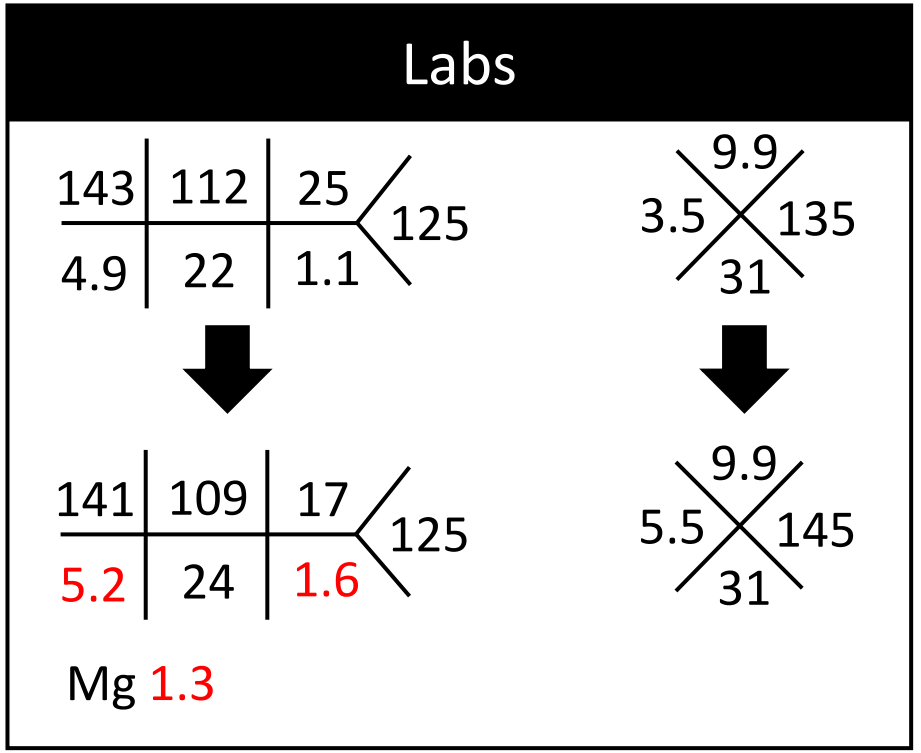
Case 2 cont…

55 yo with history of ILD s/p BOLT (3 mos ago, CMV D+/R+) presents with increased SOB and productive cough x 3 d. COVID negative. CT shows bilateral patchy GGOs. Vancomycin, cefepime, and azithromycin are started.

On HD2, their oxygenation worsens, and they are given IV furosemide 20 mg.

On HD3, patient reports a headache and new tremors. Vitals show T 36.3C, HR 93, BP 154/82, RR 24, SaO_2 94% on 2L NC.

Labs show…



What is the most likely cause of AKI?

A. Overdiuresis
B. Tacrolimus toxicity
C. Pre-renal injury from sepsis
D. Contrast induced nephropathy

MOC

What is the most likely cause of AKI?

<Poll #4 Responses>

MOC

What is the most likely cause of AKI?

A. Overdiuresis
B. Tacrolimus toxicity
C. Pre-renal injury from sepsis
D. Contrast induced nephropathy

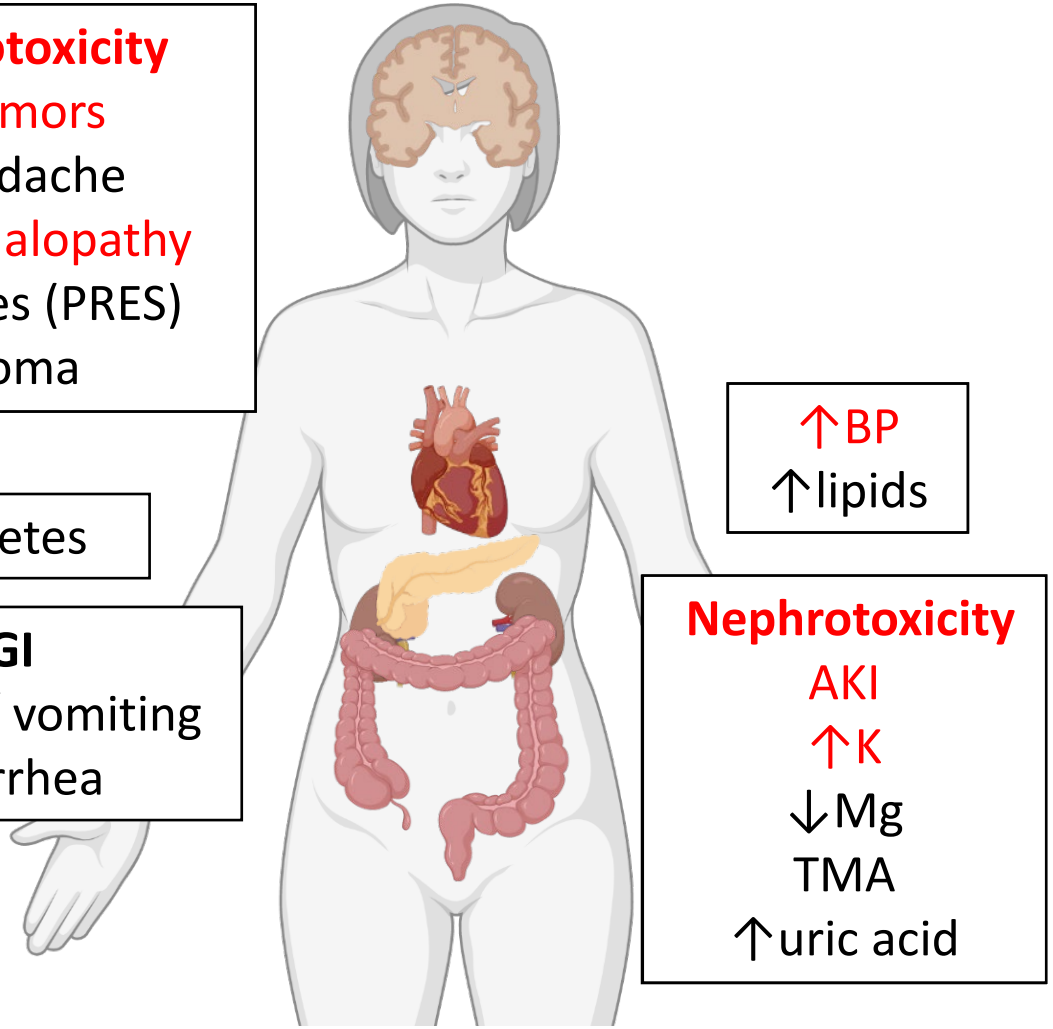
MOC

Calcineurin inhibitor toxicity

Neurotoxicity
Tremors
Headache
Encephalopathy
Seizures (PRES)
Coma

Diabetes

GI
Nausea/ vomiting
Diarrhea



↑BP
↑lipids

Nephrotoxicity
AKI
↑K
↓Mg
TMA
↑uric acid

CNIs (tacrolimus and cyclosporine) have multiple side effects

CNI toxicity can cause neurotoxicity and nephrotoxicity.
Over time, it can cause CKD and metabolic syndrome.

Images created with Biorender.com

Case 2 cont…

55 yo with history of ILD s/p BOLT (3 mos ago, CMV D+/R+) presents with increased SOB and productive cough x 3 d. COVID negative. CT shows bilateral patchy GGOs. Vancomycin, cefepime, and azithromycin are started.

On HD2, their oxygenation worsens, and they are given IV furosemide 20 mg.

On HD3, patient reports a headache and new tremors. Vitals show T 36.3C, HR 93, BP 154/82, RR 24, SaO_2 94% on 2L NC.

Labs show…

Labs

143	112	25	125
4.9	22	1.1	

9.9			
3.5			135
	31		

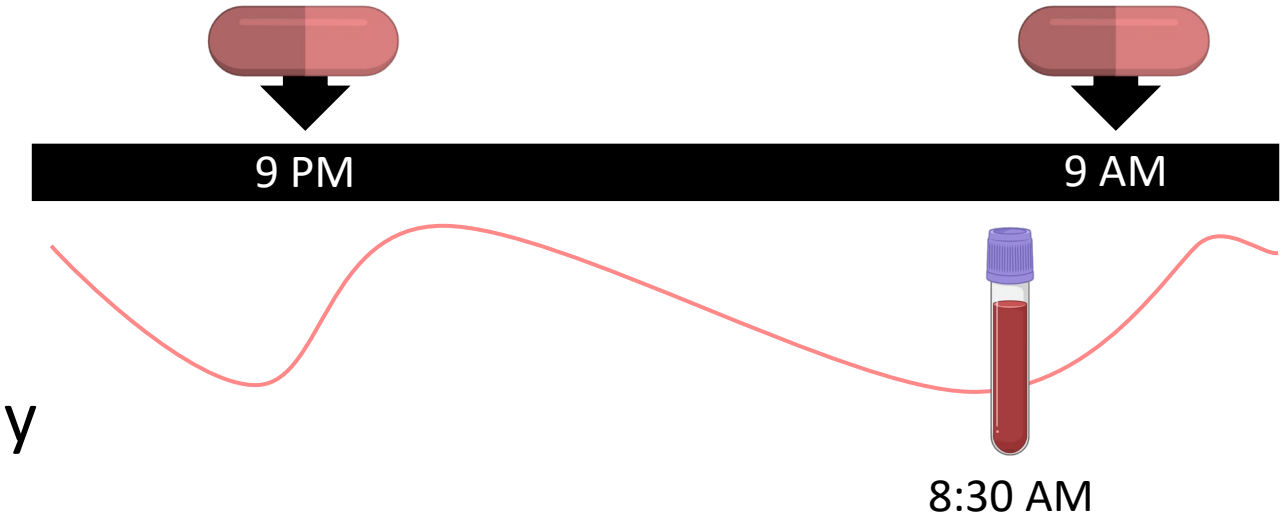
141	109	17	125
5.2	24	1.6	

9.9			
5.5			145
	31		

Mg 1.3

What is the most likely cause of AKI?

A. Overdiuresis
B. Tacrolimus toxicity
C. Pre-renal injury from sepsis
D. Contrast induced nephropathy



Tacrolimus toxicity occurs often in patients who are acutely ill and can cause AKI.

Monitor tacrolimus troughs 30 min prior to a dose (~12 h after last dose).

Case 3

64 yo with IgA nephropathy s/p deceased donor renal transplant 1.5 years ago

Case 3

64 yo with IgA nephropathy s/p DDRT (1.5 y ago, CMV D-/R-) presents after being found down. Two weeks ago, was diagnosed with COVID at urgent care and treated with nirmatrelvir-ritonavir (Paxlovid) x 5 d.

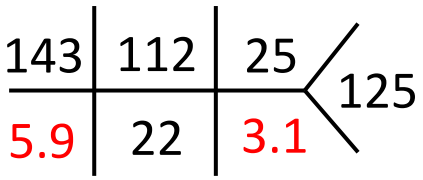
Medications

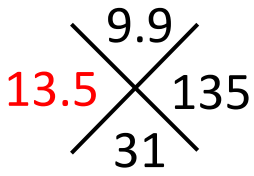
Last taken 12 h ago
Prednisone
MMF
Tacrolimus

Exam

T 36.5C, HR 113, BP 180/106
RR 22, SaO_2 97% on RA
Lungs: Clear to auscultation.
CV: Tachycardic, no murmurs
Abdomen: LLQ scar. No grimace to palpation.
Neuro: Obtunded, unable to answer questions.

Labs





Baseline Cr 1.0

UA: no leukocyte esterase, no nitrites, 0-5 WBCs, 25 RBCs
Kidney US: no hydronephrosis or bladder distention

What is your next step in evaluation?

A. Obtain urine eosinophils
B. Perform kidney biopsy
C. Obtain tacrolimus trough level
D. Place a urinary catheter

MOC

What is your next step in evaluation?

<Poll #5 Responses>

What is your next step in evaluation?

A. Obtain urine eosinophils
B. Perform kidney biopsy
C. Obtain tacrolimus trough level
D. Place a urinary catheter

MOC

Case 3

64 yo with IgA nephropathy s/p DDRT (1.5 y ago, CMV D-/R-) presents after being found down. Two weeks ago, was diagnosed with COVID at urgent care and treated with nirmatrelvir-ritonavir (Paxlovid) x 5 d.

On admit, they are hypertensive, obtunded. Labs show new AKI, hyperkalemia. UA is non-revealing and ultrasound rules out obstruction.

Tacrolimus level returns at 45. Their goal is 4-7.

CNI toxicity can cause neurotoxicity and nephrotoxicity.

Many drugs, including Paxlovid, can interact with CNIs to cause toxicity.

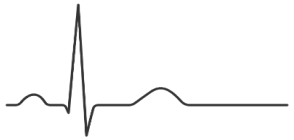
Calcineurin inhibitor drug interactions

CNIs (and mTOR inhibitors) are highly dependent on CYP3A metabolism for clearance

Drug Levels

<u>Antimicrobials</u>
Azoles
Macrolides
Antivirals (HIV meds, Paxlovid!)

<u>Antiepileptics</u>
Phenytoin
Carbamazepine
Phenobarbital



<u>Cardiac meds</u>
Diltiazem, verapamil
Amiodarone

<u>Antibiotics</u>
Nafcillin
Rifamycins

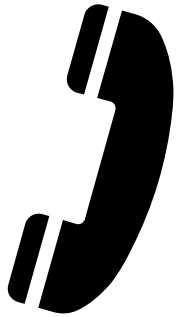
Grapefruit juice

St. John's wort

Images created with Biorender.com

Let’s take a breath…

Remember….



The Transplant Center is always here to help guide management!

Take Home Points

1. Evaluate graft dysfunction like native organ dysfunction. Additionally, consider 4 main complications: immunosuppressant side effects, rejection, infection, and surgical complications.

Take Home Points

1. Evaluate graft dysfunction like native organ dysfunction. Additionally, consider 4 main complications: immunosuppressant side effects, rejection, infection, and surgical complications.
2. Time since transplant (a surrogate for level of immunosuppression) impacts the risk of certain infections.

Take Home Points

1. Evaluate graft dysfunction like native organ dysfunction. Additionally, consider 4 main complications: immunosuppressant side effects, rejection, infection, and surgical complications.
2. Time since transplant (a surrogate for level of immunosuppression) impacts the risk of certain infections.
3. Maintain a high level of suspicion for infection. Immunosuppression can blunt classic symptoms of infection.

Take Home Points

1. Evaluate graft dysfunction like native organ dysfunction. Additionally, consider 4 main complications: immunosuppressant side effects, rejection, infection, and surgical complications.
2. Time since transplant (a surrogate for level of immunosuppression) impacts the risk of certain infections.
3. Maintain a high level of suspicion for infection. Immunosuppression can blunt classic symptoms of infection.
4. Do not routinely hold immunosuppression. Dose CNIs consistently and time troughs (~12 hours after last dose).

Take Home Points

1. Evaluate graft dysfunction like native organ dysfunction. Additionally, consider 4 main complications: immunosuppressant side effects, rejection, infection, and surgical complications.
2. Time since transplant (a surrogate for level of immunosuppression) impacts the risk of certain infections.
3. Maintain a high level of suspicion for infection. Immunosuppression can blunt classic symptoms of infection.
4. Do not routinely hold immunosuppression. Dose CNIs consistently and time troughs (~12 hours after last dose).
5. Many drugs affect CNI levels. CNI toxicity may present with neurotoxicity and nephrotoxicity.

Take Home Points

1. Evaluate graft dysfunction like native organ dysfunction. Additionally, consider 4 main complications: immunosuppressant side effects, rejection, infection, and surgical complications.
2. Time since transplant (a surrogate for level of immunosuppression) impacts the risk of certain infections.
3. Maintain a high level of suspicion for infection. Immunosuppression can blunt classic symptoms of infection.
4. Do not routinely hold immunosuppression. Dose CNIs consistently and time troughs (~12 hours after last dose).
5. Many drugs affect CNI levels. CNI toxicity may present with neurotoxicity and nephrotoxicity.

Clinical Pearls

Medications

- Avoid Paxlovid in patients on CNIs!
- Ca^{2+} channel blockers, azoles ↑ CNI levels. Antiepileptics ↓ CNI levels.
- CNI levels can ↑ in acute illness.
- mTOR inhibitors impair wound healing.
- Myelosuppression is greatest with valganciclovir > MMF >> TMP/SMX > CNI.

Kidney transplant

- Treat symptomatic UTI as complicated UTI.
- Routinely treating asymptomatic bacteriuria is no longer recommended.

Infectious Disease

- Consider donor-derived infections in the early post-transplant period.
- Treatment for recent rejection (or any ↑ immunosuppression) shifts risk profile for infections and malignancies.
- Note D/R CMV status! CMV infection occurs with ↑ immunosuppression but is less likely several years post-transplant.
- ↑ immunosuppression increases risk of infection-related malignancies (PTLD, squamous cell cancer, etc.)
- Skin lesions can also be due to opportunistic infections – *Cryptococcus*, molds, *Nocardia*, etc.

Images created with Biorender.com

Clinical Pearls

Lung transplant

- Have a low threshold to check an extended respiratory viral panel.
- Lung transplants are the most likely to reject of all SOT.
- Dry lungs are happy lungs! Lung transplants are prone to pulmonary edema due to lack of lymphatics. Have a low threshold to diurese.
- Signs and symptoms of acute rejection are nonspecific and can mimic infection.
- Consider prior colonization of lungs and sinuses to guide antibiotic choice.

Liver transplant

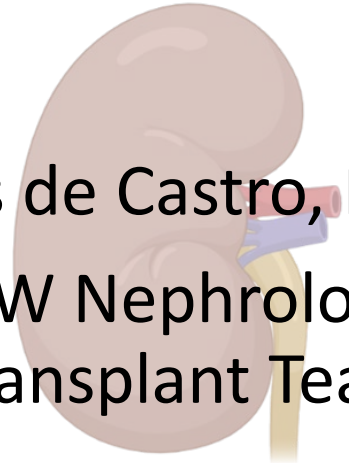
- Liver transplants are least likely to reject.
- Obtain a liver duplex in the evaluation of new liver dysfunction.

Heart transplant

- Transplanted hearts are denervated. Patients have chronic tachycardia.
- Ischemia may not produce chest pain (due to denervation).
- Involve Transplant Cardiology!

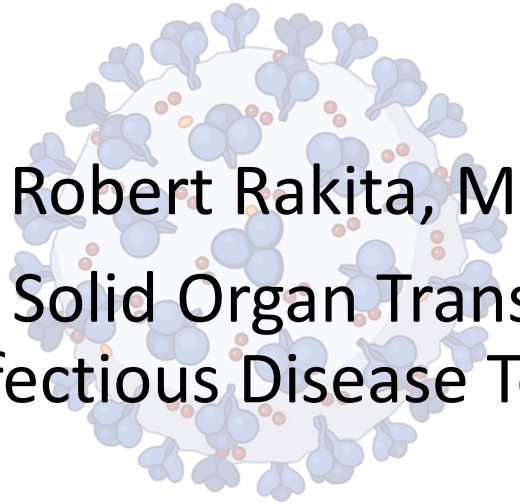
Images created with Biorender.com

Special thanks to our Transplant Specialists!



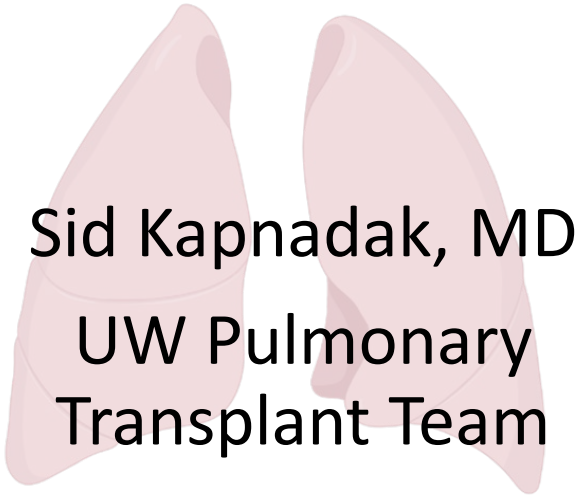
Iris de Castro, MD

UW Nephrology Transplant Team



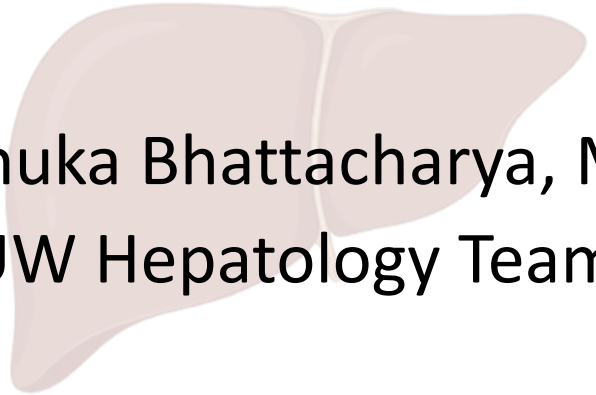
Robert Rakita, MD

UW Solid Organ Transplant Infectious Disease Team



Sid Kapnadak, MD

UW Pulmonary Transplant Team

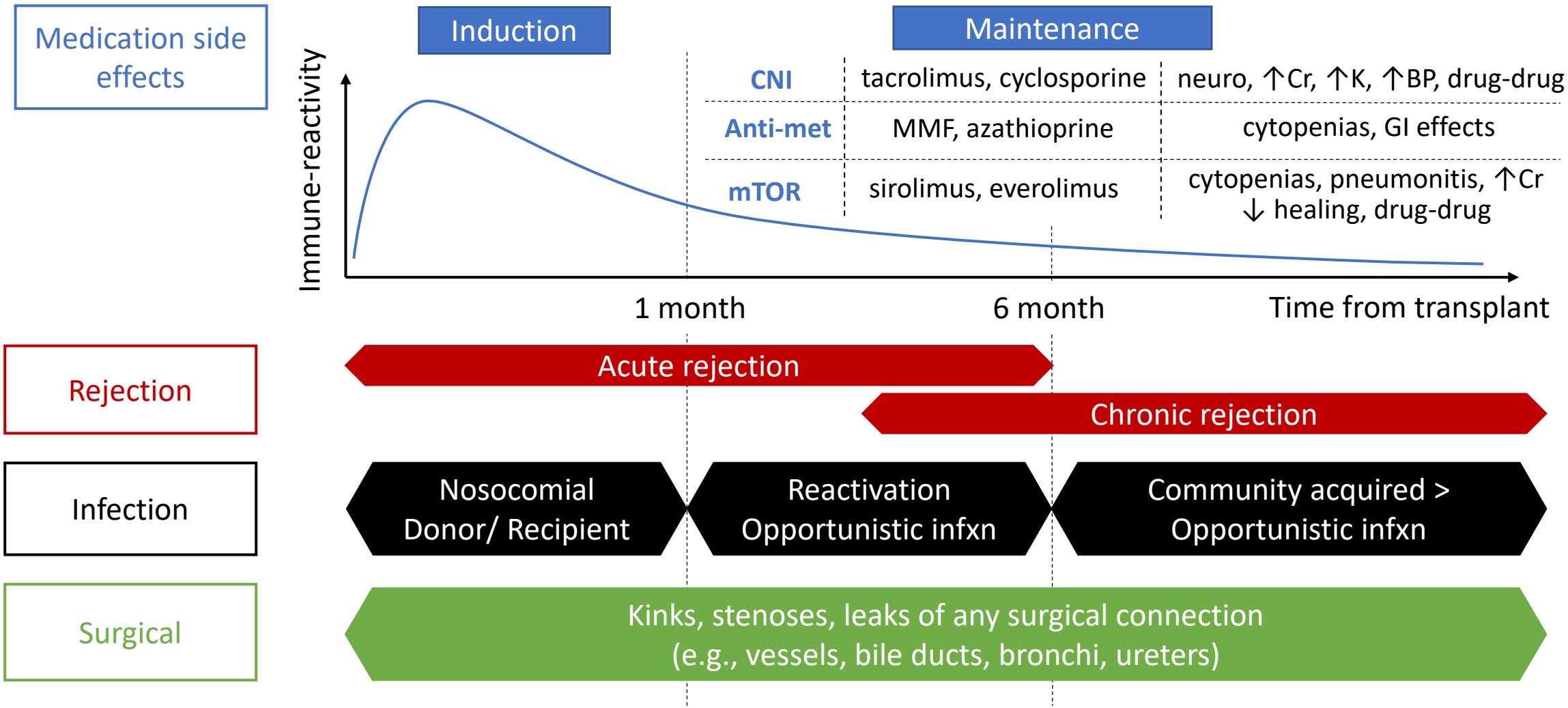


Renuka Bhattacharya, MD

UW Hepatology Team

Images created with Biorender.com

Questions?


Medication side effects
Induction
Maintenance
Immune-reactivity
CNI
tacrolimus, cyclosporine
neuro, ↑Cr, ↑K, ↑BP, drug-drug
Anti-met
MMF, azathioprine
cytopenias, GI effects
mTOR
sirolimus, everolimus
cytopenias, pneumonitis, ↑Cr
↓ healing, drug-drug
1 month
6 month
Time from transplant
Rejection
Acute rejection
Chronic rejection
Infection
Nosocomial
Donor/ Recipient
Reactivation
Opportunistic infxn
Community acquired >
Opportunistic infxn
Surgical
Kinks, stenoses, leaks of any surgical connection
(e.g., vessels, bile ducts, bronchi, ureters)