2022 ACP WASHINGTON CHAPTER ANNUAL MEETING – INPATIENT PRECOURSE

Inpatient Management of Solid Organ Transplant Patients

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UW Medicine

Disclosures

- We have no disclosures

Thank you for your care of transplant patients!

Goals

Train Transplant Medicine Specialists

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

Call the Transplant Center early!
They want to help!

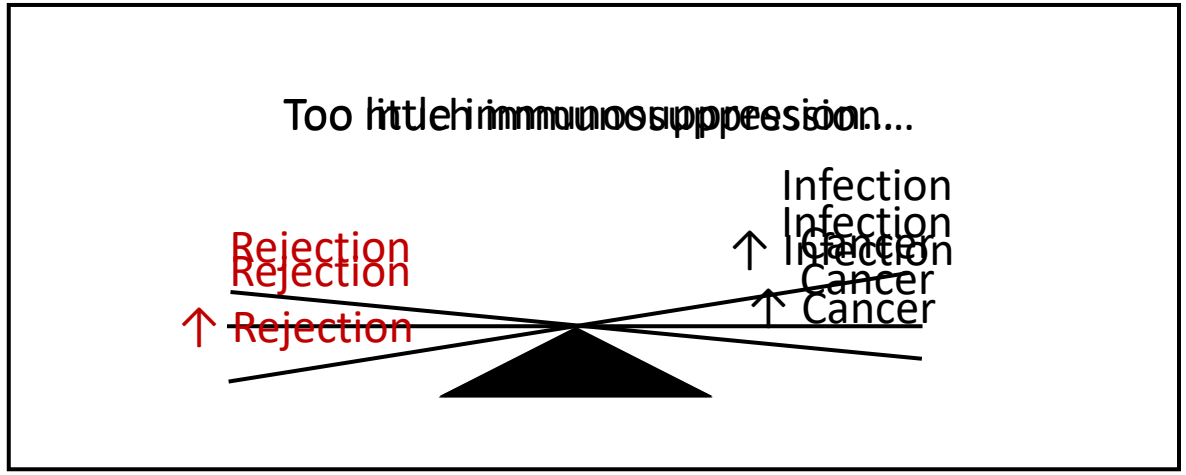
Objectives

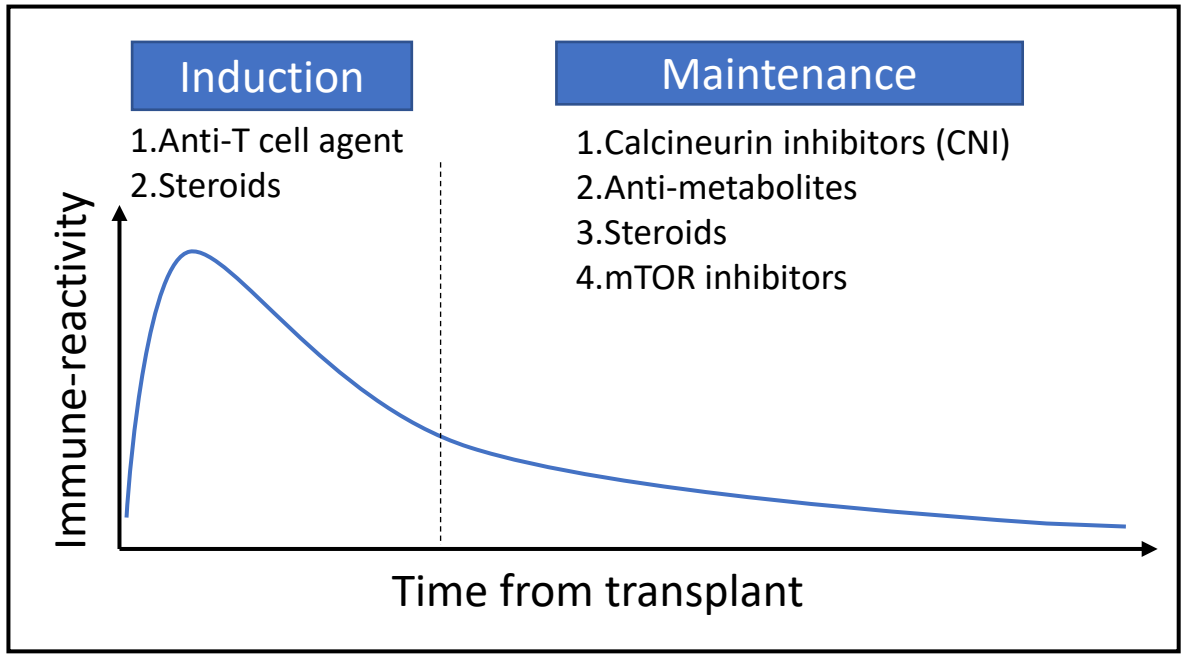
By the end of this talk, you will be able to…

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

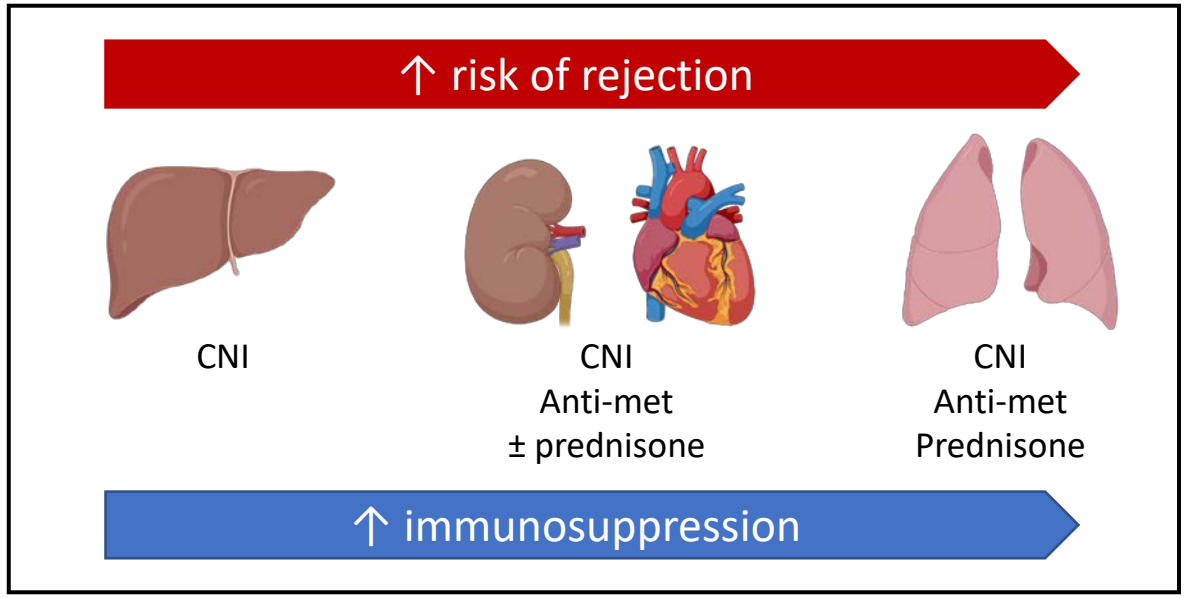
- Core principle of Transplant Medicine is balancing immunosuppression
- The amount of immunosuppression depends on:
  - Time from transplant

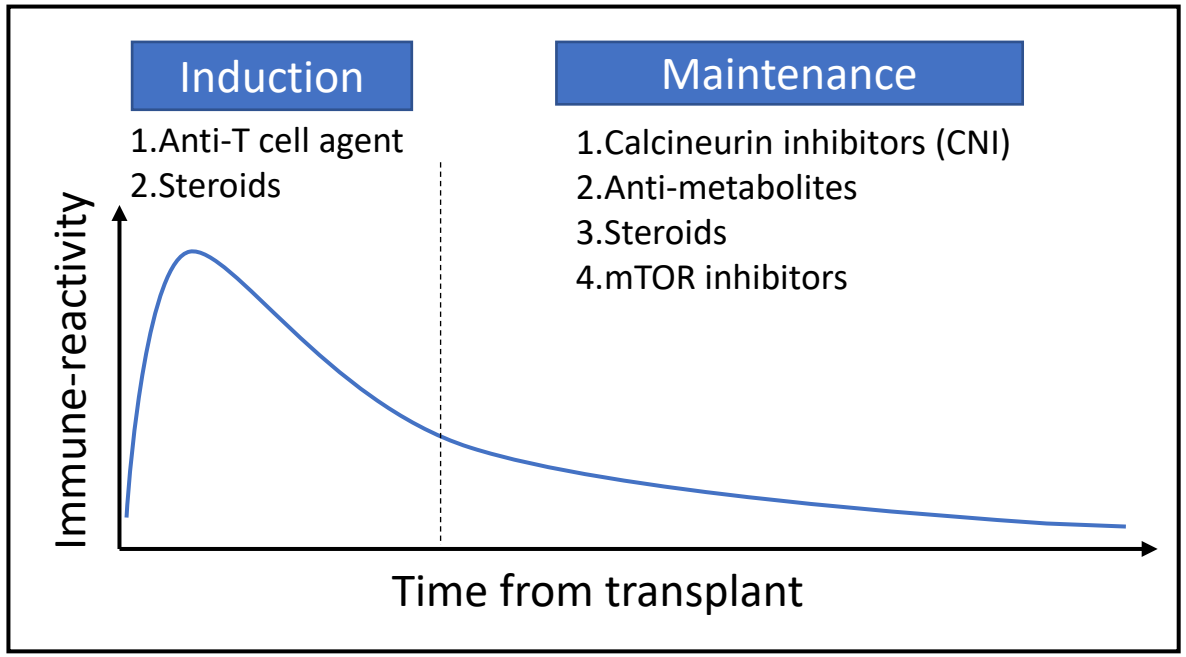




Transplant Basics

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





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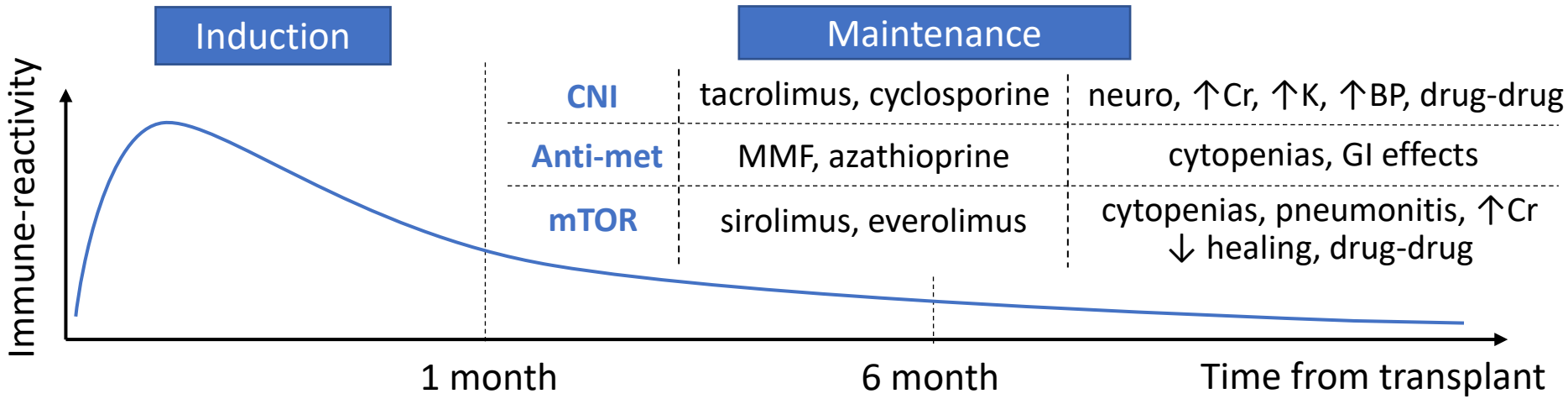
Complications

Medication side effects



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)

Case 1

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

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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	

	9.9	
13.5		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 urine 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 urine tox screen**
B. **Acute hepatitis panel**
C. **RUQ ultrasound**
D. **Liver ultrasound with duplex**
E. **Verify medication history**
F. **Cyclosporine trough**
G. **CMV PCR**

63 yo with a history of ETOH cirrhosis s/p liver transplant (5 y ago, CMV D+/R-) on cyclosporine who presents with 4 d of malaise, abdominal pain, nausea/ vomiting.

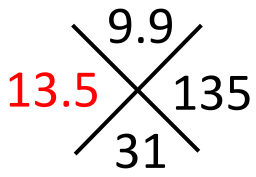
Exam

T 37.9C, HR 113
Skin: Jaundiced.

Labs

BMP normal

AST 232 Tbili 4.3
ALT 350 ALP 232



What are your next steps in evaluation?

A. Serum and urine 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 work-up 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 urine tox screen

B. Acute hepatitis panel

C. RUQ ultrasound

D. Liver ultrasound with duplex

E. Verify medication history

F. Cyclosporine trough

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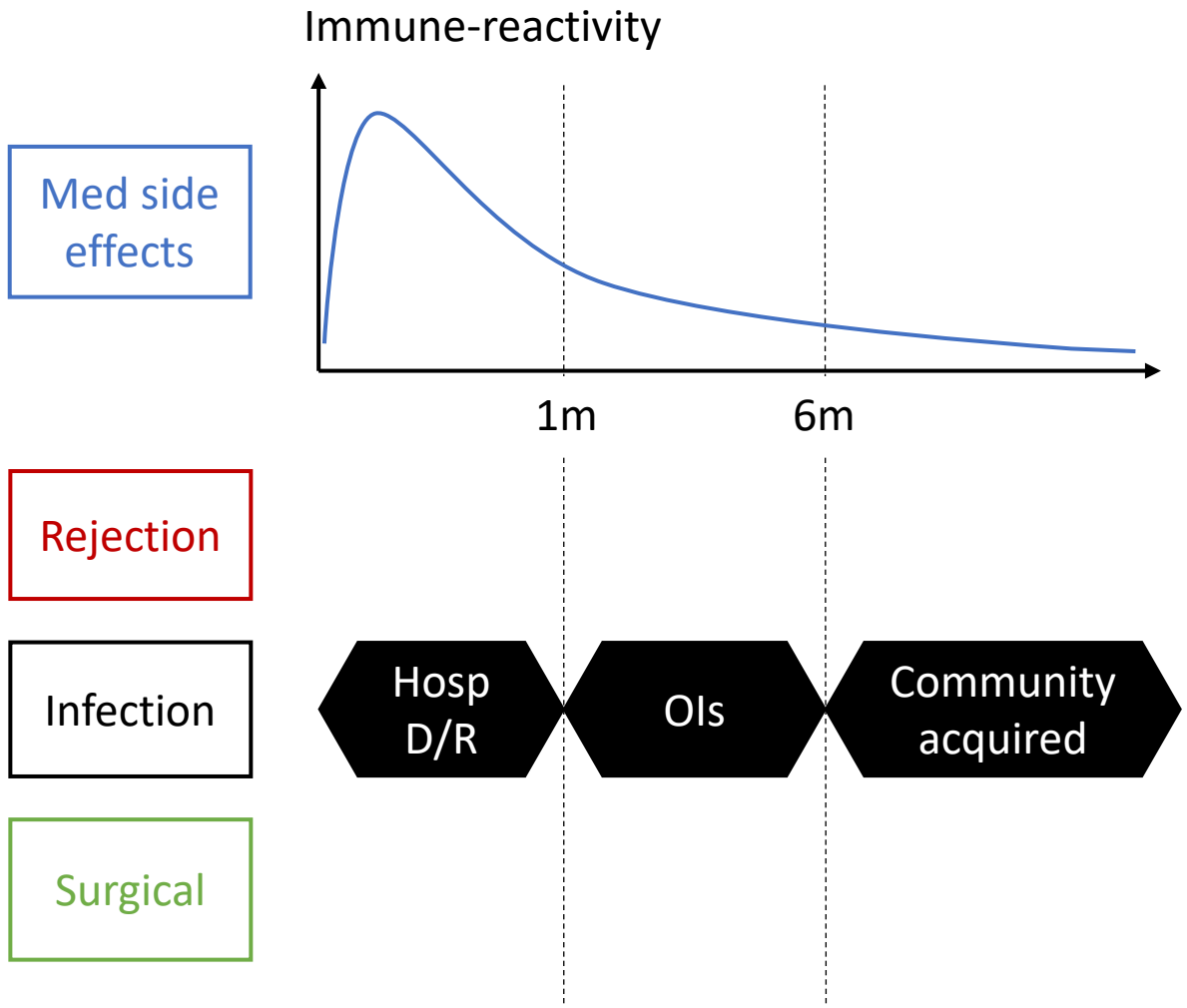

What are your next steps in evaluation?

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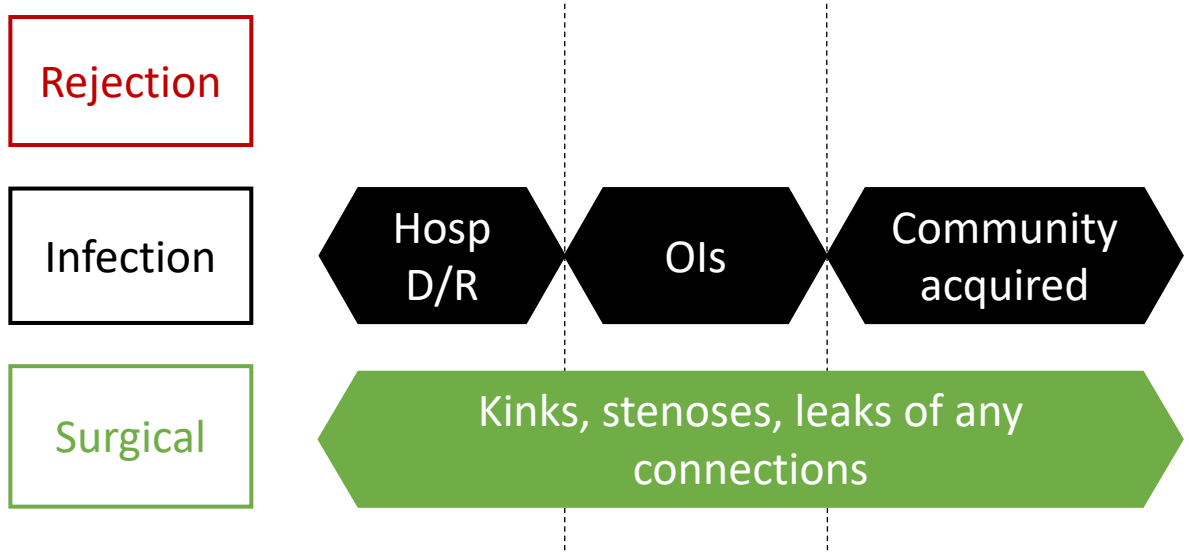
G. CMV PCR

Evaluate for anatomic complications (vascular stenoses) using **duplex** in patients presenting with graft dysfunction.



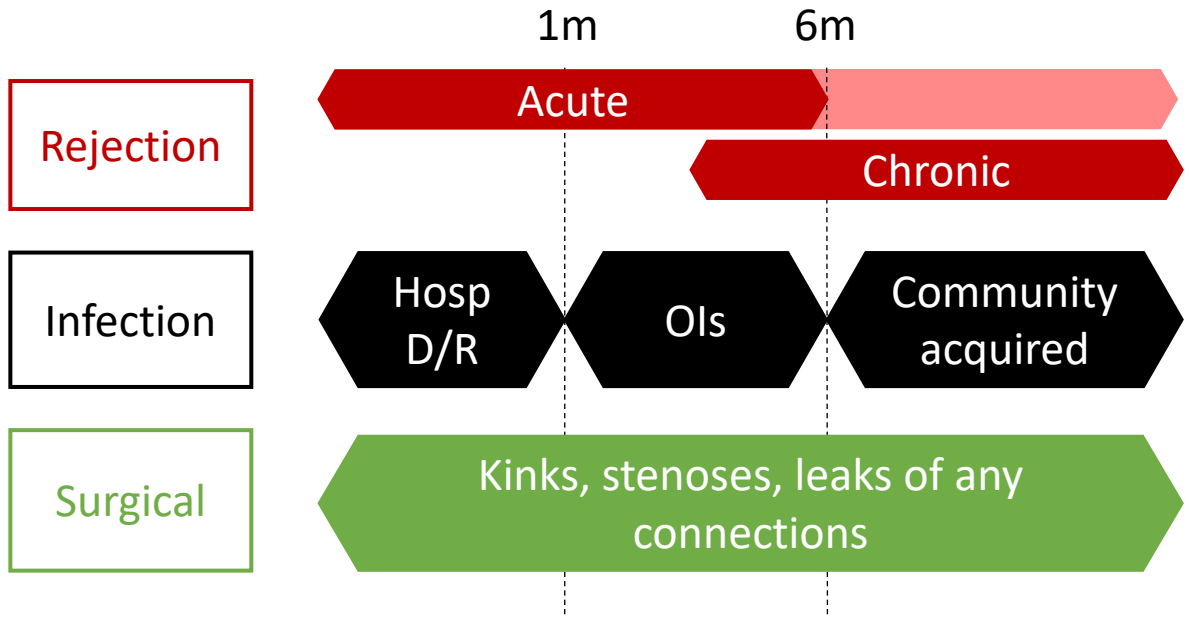
Sanyal R, et al. Indian J Radiol Imaging, 2014

What are your next steps in evaluation?

A. Serum and urine 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.

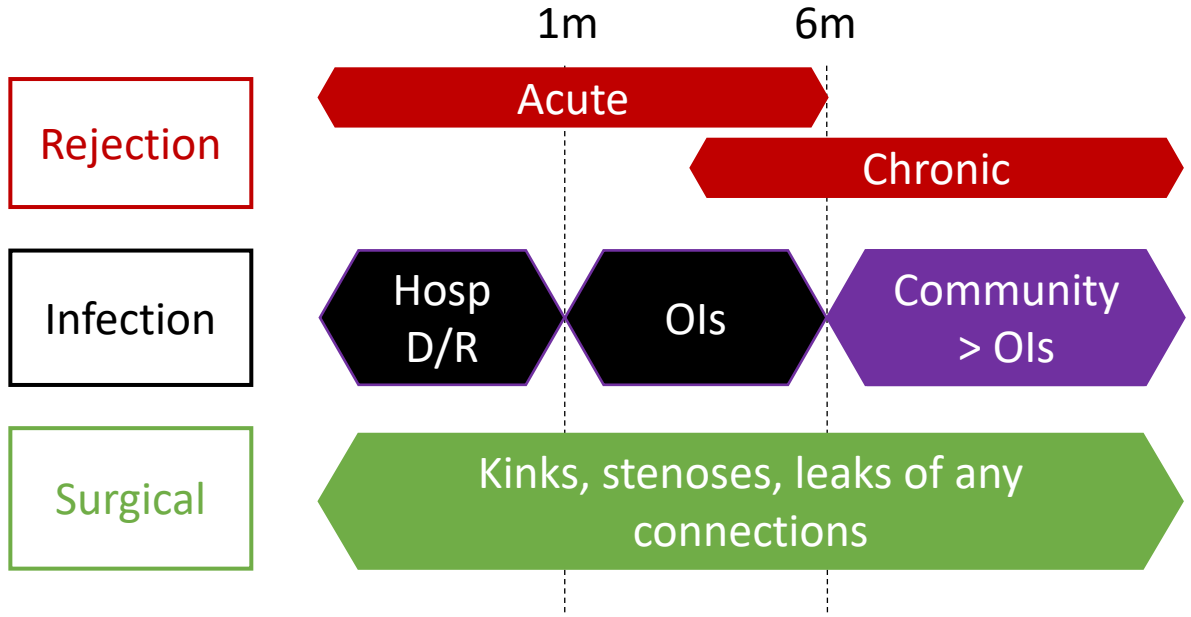
Acute rejection is most common <6 mos. Later, it occurs with under-immunosuppression.



What are your next steps in evaluation?

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

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



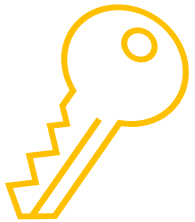
Case 1

63 yo with a history of alcohol-related cirrhosis s/p liver transplant (5 y ago, CMV D+/R-) who presents with acute liver injury.

Medication reconciliation showed no fills on cyclosporine for 2 months. **Cyclosporine trough was undetectable**.

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

Key Recap



- Initial evaluation of graft dysfunction should include typical work-up for native organ dysfunction.
- Evaluate for anatomic complications (e.g., vascular stenoses) using **duplex** (not just RUQ US).
- Acute rejection is most common in the first 6 months but can occur later with underimmunosuppression.

Case 2

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

UW Medicine

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?

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

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

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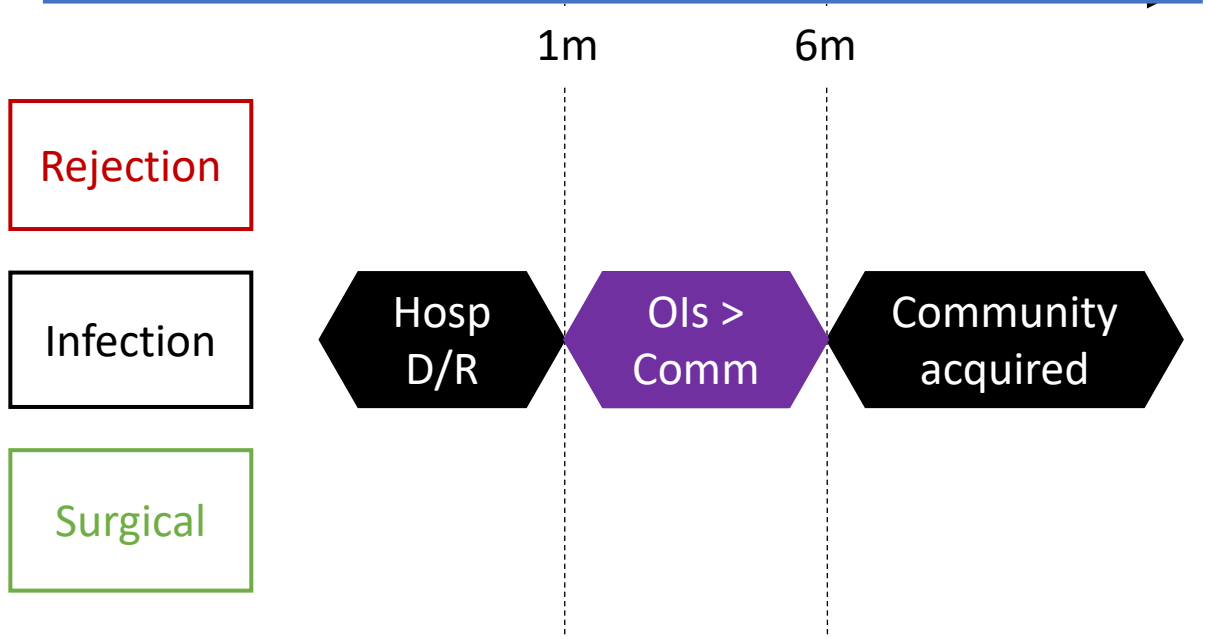
C. Consult Pulmonology to consider bronchoscopy

D. Send serum CMV PCR

E. CT chest

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



Dulek & Mueller, *Clin Transplant*. 2019

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A. **Send extended viral PCR**

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

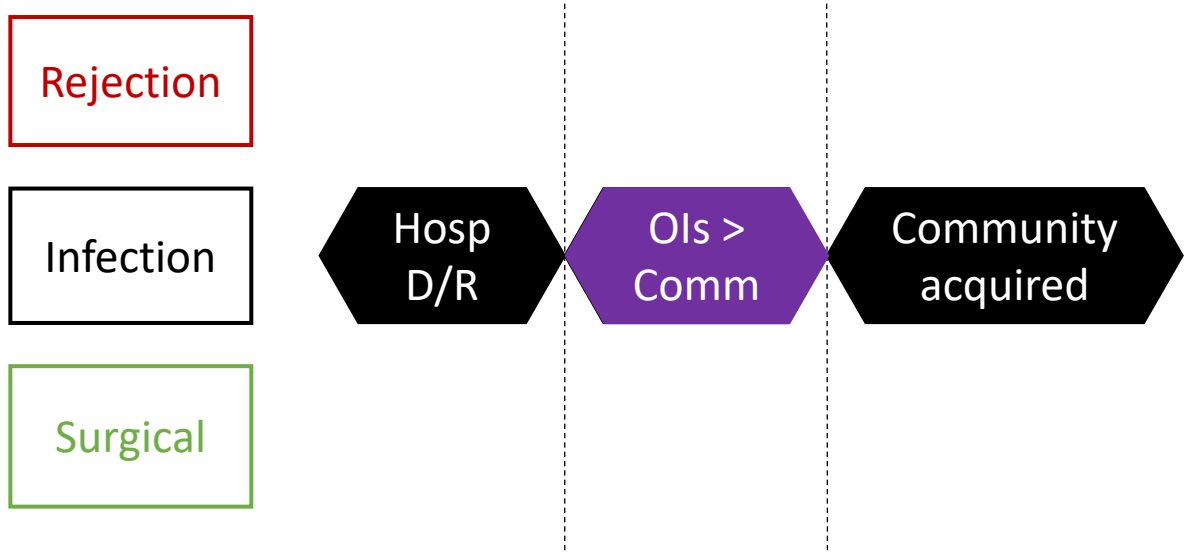
C. Consult Pulmonology to consider bronchoscopy

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.



Dulek & Mueller, *Clin Transplant*. 2019; Nosotti M et al, *J Thorac Dis,* 2018.

What are your next steps in evaluation?

A. Send extended viral PCR

B. Send sputum culture, urinary Legionella and Strep Ag

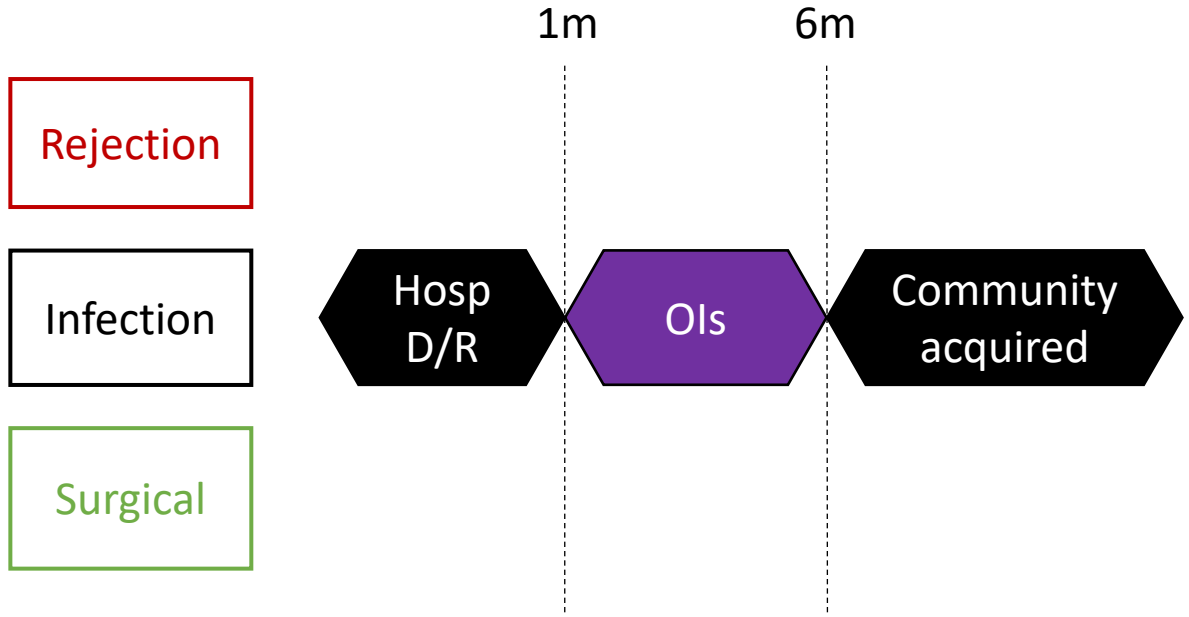
C. Consult Pulmonology to consider bronchoscopy

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 infection.



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What are your next steps in evaluation?

A. Send extended viral PCR

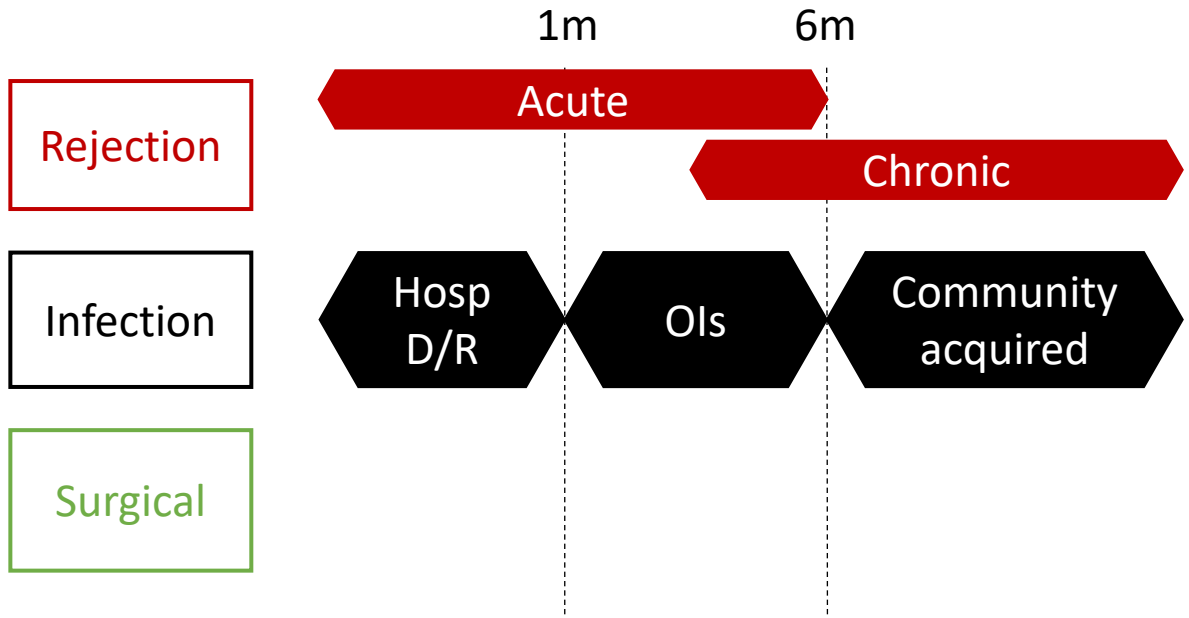
B. Send sputum culture, urinary Legionella and Strep Ag

C. Consult Pulmonology to consider bronchoscopy

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.



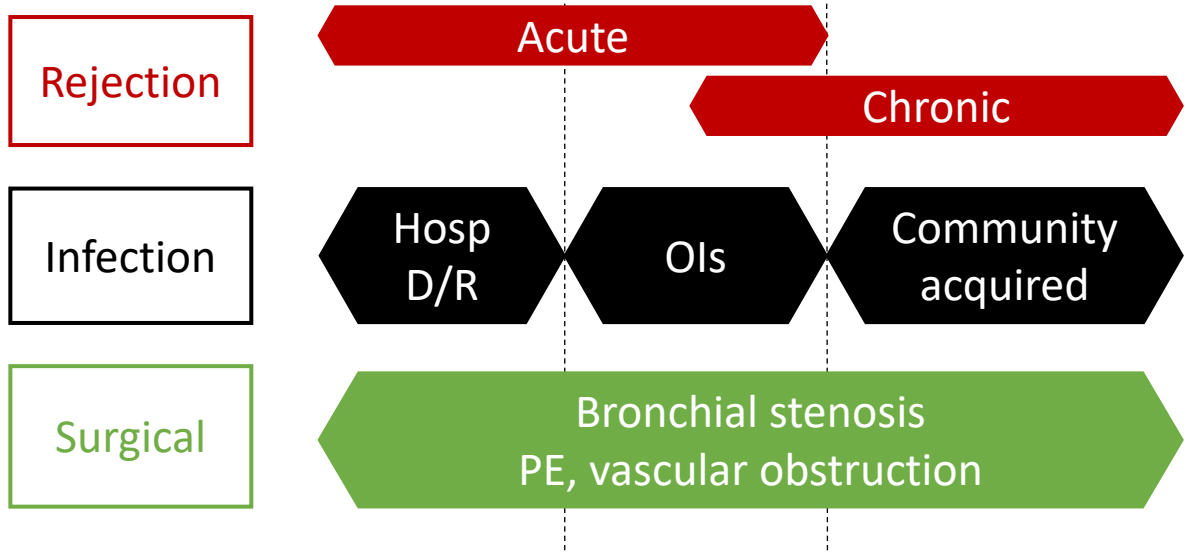
Dulek & Mueller, *Clin Transplant*. 2019

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 for CMV PCR
E. 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.



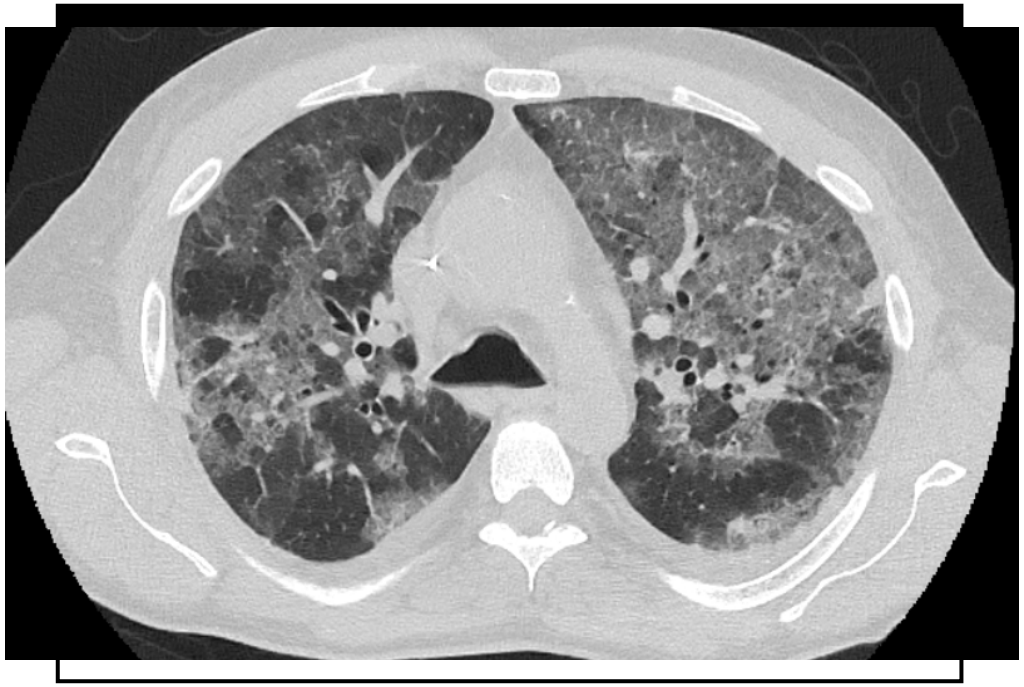
Dulek & Mueller, *Clin Transplant*. 2019

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

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.

What is your next step in management?

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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.

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.

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.~~

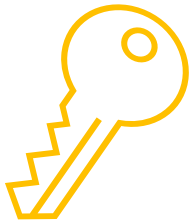
D. Start vancomycin + cefepime + azithromycin.

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

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

MOC, Dulek & Mueller, *Clin Transplant*. 2019

Key Recap



- Immunosuppression may blunt fever or leukocytosis.
- Viral infections are common and can cause significant morbidity and mortality after lung transplant.
- Note donor and recipient CMV status! CMV can reactivate and cause multiorgan damage.
- Do NOT routinely change immunosuppression without discussing with the Transplant team.
- Lung transplant patients are prone to pulmonary edema! Manage volume judiciously.

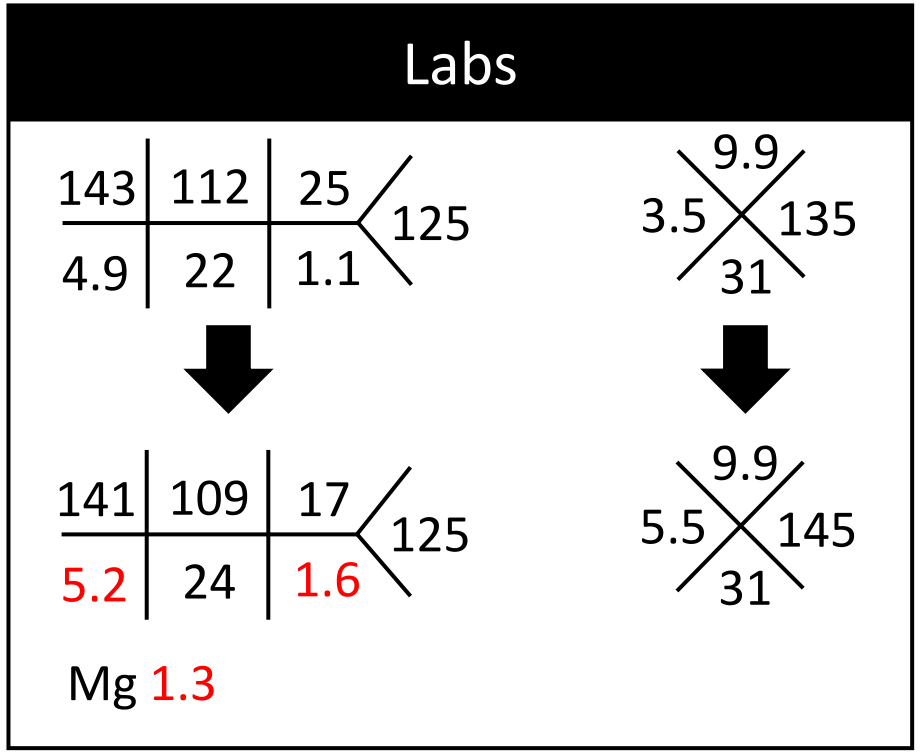
Case 2 cont…

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

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A. Overdiuresis

B. Tacrolimus toxicity

C. Pre-renal injury from sepsis

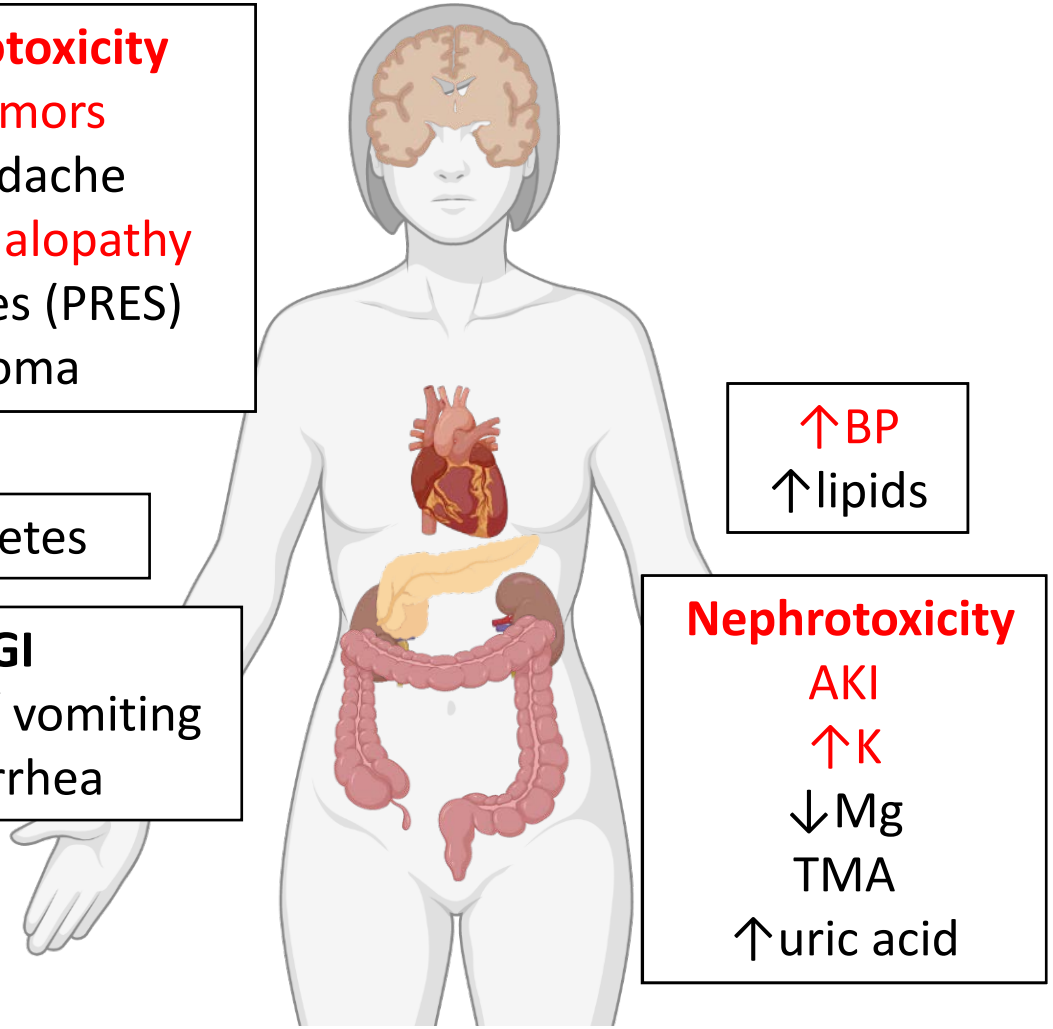
D. Contrast induced nephropathy

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.

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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	

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	31		

Mg 1.3

What is the most likely cause of AKI?

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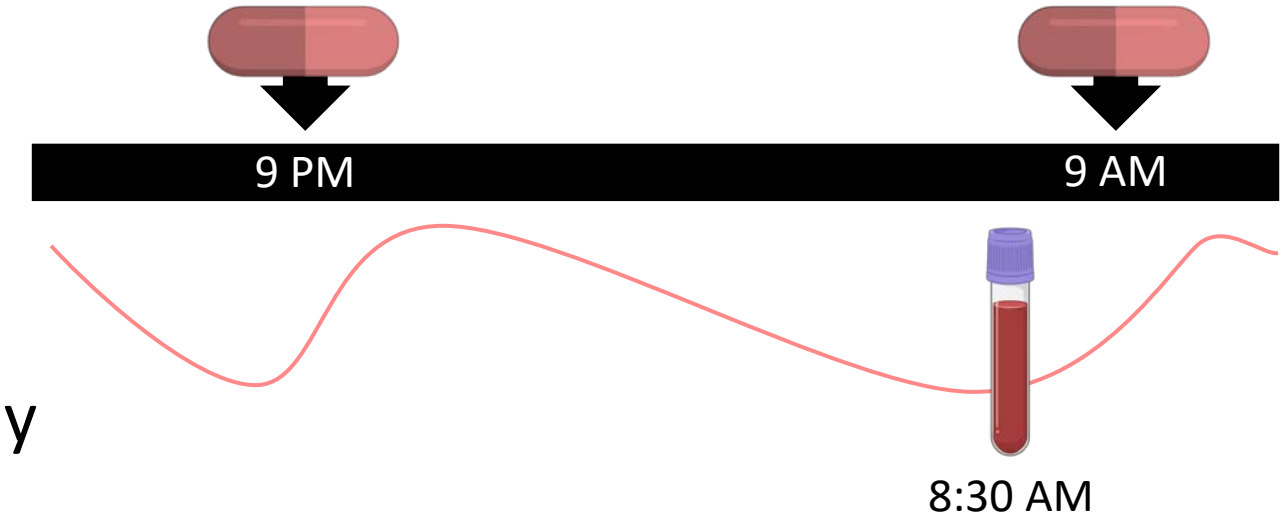

Tacrolimus toxicity is a common cause of AKI in patients who are acutely ill.

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

Case 3

64-year-old with history of IgA nephropathy who underwent deceased donor renal transplant 1.5 years ago

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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.

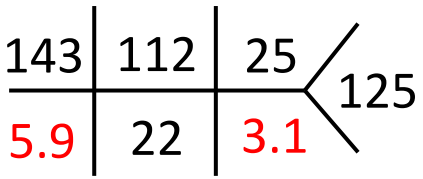
Medications

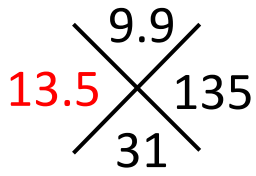
Last taken 12 h ago
Prednisone
MMF
Tacrolimus

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: Graft palpable in LLQ. No grimace.
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

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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. Ultrasound rules out obstruction and renal duplex shows normal vascular flow.

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

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

Grapefruit juice

<u>Antiepileptics</u>
Phenytoin
Carbamazepine
Phenobarbital

<u>Antibiotics</u>
Nafcillin
Rifamycins

St. John's wort

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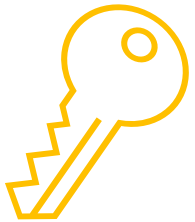
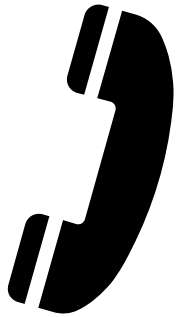
Key Recap



- Calcineurin inhibitors can cause neurotoxicity and nephrotoxicity.
- Acute illness can cause elevated CNI levels leading to AKI.
- Dose CNI consistently (every 12 hours) and check a trough level early in the admission.
- CNIs (and mTOR inhibitors) have many drug-drug interactions!

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.
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. CNIs can cause 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.

Liver transplant

- Obtain a liver duplex in the evaluation of new liver dysfunction.
- Increased vascular resistance on duplex may be an early sign of rejection.

Infectious Disease

- Consider donor-derived infections in the early post-transplant period.
- Note D/R CMV status! CMV infection can cause multi-organ dysfunction.
- Treatment for recent rejection (or any ↑ immunosuppression) shifts risk profile for infections and malignancies.
- ↑ immunosuppression increases risk of infection-related malignancies (PTLD, squamous cell cancer, etc.)
- Skin lesions can also be due to opportunistic infections – *Nocardia*, *Cryptococcus*, other fungi, etc.

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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.

Kidney transplant

- Treat symptomatic UTI as complicated UTI. Assess for (lower quadrant) graft tenderness.
- Routinely treating asymptomatic bacteriuria is no longer recommended.
- Obtain a duplex in the evaluation of AKI.

Heart transplant

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

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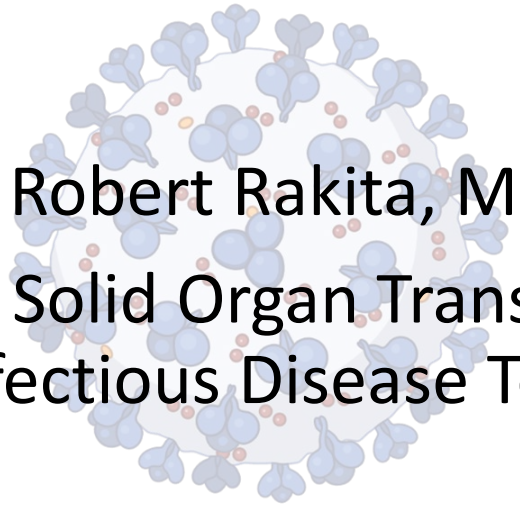
UW Medicine

Special thanks to our Transplant Specialists!

Iris de Castro, MD

UW Transplant Nephrology Team



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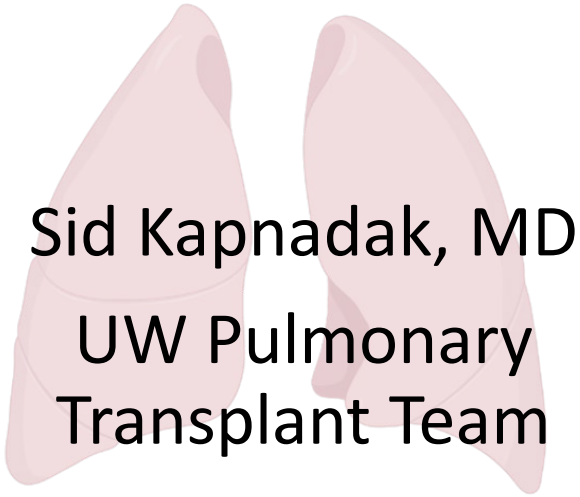

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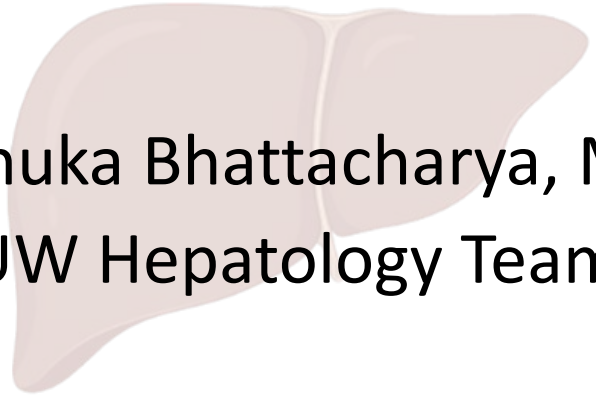

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Additional thanks to…

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UW Medicine
VALLEY
MEDICAL CENTER

Taylor Gabriel, MD

Valley Family Medicine Residents!

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Questions?

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Thank You

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