Inpatient Management of Solid Organ Transplant Patients

2022 ACP Washington Chapter Annual Meeting – Inpatient Precourse
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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

↑ risk of rejection

↑ immunosuppression

Induction
1. Anti-T cell agent
2. Steroids

Maintenance
1. Calcineurin inhibitors (CNI)
2. Anti-metabolites
3. Steroids
4. mTOR inhibitors

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Complications

**Induction**
- CNI: tacrolimus, cyclosporine
- Anti-met: MMF, azathioprine
- mTOR: sirolimus, everolimus

**Maintenance**
- CNI: neuro, ↑Cr, ↑K, ↑BP, drug-drug interactions
- Anti-met: cytopenias, Gl effects
- mTOR: cytopenias, pneumonitis, ↑Cr, ↓ healing, drug-drug

**Rejection**
- Acute rejection
- Chronic rejection

**Infection**
- Nosocomial
- Reactivation
- Community acquired > Opportunistic infxn

**Surgical**
- Kinks, stenoses, leaks of any surgical connection (e.g., vessels, bile ducts, bronchi, ureters)

**Medication side effects**
- Anti-met: MMF, azathioprine cytopenias, GI effects
- CNI: tacrolimus, cyclosporine
- mTOR: sirolimus, everolimus

**Time from transplant**
- 1 month
- 6 month
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.

<table>
<thead>
<tr>
<th>Medications</th>
<th>Exam</th>
<th>Labs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclosporine</td>
<td>T 37.9C, HR 113, BP 110/56&lt;br&gt;RR 22, SaO₂ 97% on RA&lt;br&gt;Lungs: Clear to auscultation.&lt;br&gt;CV: Tachycardic, no murmurs&lt;br&gt;Abdomen: RUQ chevron scar.&lt;br&gt;Skin: Jaundiced.</td>
<td>143 3.9 25&lt;br&gt;112 22 1.1&lt;br&gt;25 125 13.5&lt;br&gt;SaO₂ 97% on RA&lt;br&gt;Lungs: Clear to auscultation.</td>
</tr>
</tbody>
</table>
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
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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
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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.

- **Rejection**
- **Infection**
- **Surgical**

- **Hosp D/R**
- **Ols**
- **Community acquired**

Kinks, stenoses, leaks of any connections
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.

Kinks, stenoses, leaks of any connections

1m  
Acute  
Hosp D/R

6m  
Chronic  
Ols

Community > OIs

Rejection  
Infection  
Surgical
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.

<table>
<thead>
<tr>
<th>Medications</th>
<th>Exam</th>
<th>Labs</th>
</tr>
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<tbody>
<tr>
<td>Prednisone</td>
<td>T 37C, HR 113, BP 110/56</td>
<td>143 3.5 9.9</td>
</tr>
<tr>
<td>MMF</td>
<td>RR 28, SaO₂ 87% on RA</td>
<td>112 22 31</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Lungs: ↑WOB, diffuse crackles, no wheezing</td>
<td>25 1.1 135</td>
</tr>
<tr>
<td>TMP/SMX</td>
<td>CV: Tachycardic, no JVD or LE edema</td>
<td>125</td>
</tr>
<tr>
<td>Valganciclovir</td>
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</table>

- 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 \textbf{37^\circ}C, HR 113, BP 110/56
RR 28, SaO\textsubscript{2} 87\% on RA

Labs

\begin{tabular}{|c|c|c|}
\hline
9.9 & \textbf{3.5} & 135 \\
\textbf{31} & & \\
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\end{tabular}
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 37°C, HR 113, BP 110/56
RR 28, SaO₂ 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.

- **Rejection**
- **Acute**
- **Chronic**
- **Infection**
- **Hosp D/R**
- **Ols**
- **Community acquired**
- **Surgical**
- **Bronchial stenosis**
- **PE, vascular obstruction**
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.
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?

<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.
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What is your next step in management?

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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.
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).
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 36.3°C, HR 93, BP 154/82, RR 24, SaO₂ 94% on 2L NC. Labs show...

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<tr>
<td><strong>Labs</strong></td>
<td>143</td>
<td>112</td>
<td>25</td>
<td>125</td>
<td>3.5</td>
<td>135</td>
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<td><strong>Na</strong></td>
<td>4.9</td>
<td>22</td>
<td>1.1</td>
<td>125</td>
<td>3.5</td>
<td>31</td>
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<td><strong>Ca</strong></td>
<td>141</td>
<td>109</td>
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<td>125</td>
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<tr>
<td><strong>K</strong></td>
<td>5.2</td>
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<td>1.6</td>
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<td><strong>Mg</strong></td>
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<td>1.3</td>
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What is the most likely cause of AKI?

A. Overdiuresis
B. Tacrolimus toxicity
C. Pre-renal injury from sepsis
D. Contrast induced nephropathy
What is the most likely cause of AKI?

<Poll #4 Responses>
What is the most likely cause of AKI?

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

**GI**
- Nausea/vomiting
- Diarrhea

**Nephrotoxicity**
- AKI
- ↑K
- ↓Mg
- TMA
- ↑uric acid
- ↑BP
- ↑lipids

CNIs (tacrolimus and cyclosporine) have multiple side effects.

CNI toxicity can cause neurotoxicity and nephrotoxicity. Over time, it can cause CKD and metabolic syndrome.
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, SaO₂ 94% on 2L NC.

Labs show...

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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.

<table>
<thead>
<tr>
<th>Medications</th>
<th>Exam</th>
<th>Labs</th>
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<tbody>
<tr>
<td><em>Last taken 12 h ago</em></td>
<td>T 36.5°C, HR 113, BP 180/106&lt;br&gt;RR 22, SaO₂ 97% on RA&lt;br&gt;Lungs: Clear to auscultation.&lt;br&gt;CV: Tachycardic, no murmurs&lt;br&gt;Abdomen: LLQ scar. No grimace to palpation.&lt;br&gt;Neuro: Obtunded, unable to answer questions.</td>
<td>143</td>
</tr>
<tr>
<td>Prednisone</td>
<td>112</td>
<td>22</td>
</tr>
<tr>
<td>MMF</td>
<td>25</td>
<td>3.1</td>
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<tr>
<td>Tacrolimus</td>
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<td>31</td>
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</table>

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
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
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

Antimicrobials
Azyoles
Macrolides
Antivirals (HIV meds, Paxlovid!)

Cardiac meds
Diltiazem, verapamil
Amiodarone

Antiepileptics
Phenytoin
Carbamazepine
Phenobarbital

Antibiotics
Nafcillin
Rifamycins

Grapefruit juice
St. John’s wort
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

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2. Time since transplant (a surrogate for level of immunosuppression) impacts the risk of certain infections.
Take Home Points

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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

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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

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5. Many drugs affect CNI levels. CNI toxicity may present with neurotoxicity and nephrotoxicity.
Take Home Points

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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.

**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.

**Kidney transplant**

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

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Questions?
Induction

Maintenance

Immune-reactivity

Time from transplant

1 month

6 month

Medication side effects

Acute rejection

Chronic rejection

Rejection

Infection

Surgical

Nosocomial

Donor/Recipient

Reactivation

Opportunistic infection

Community acquired > Opportunistic infection

Kinks, stenoses, leaks of any surgical connection (e.g., vessels, bile ducts, bronchi, ureters)

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

Medication side effects

Anti-met

MMF, azathioprine
cytopenias, GI effects

mTOR

sirolimus, everolimus
cytopenias, pneumonitis, ↑Cr
↓ healing, drug-drug