Medical management of the Liver Transplant patient

Nikolaos T. Pyrsopoulos, MD, PhD, MBA, FACP, AGAF
Chief of Gastroenterology and Hepatology
Medical Director Liver Transplantation
Rutgers- New Jersey Medical School
University Hospital

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- **Advisory Board**: Vital Therapies

OLTx Milestones

- 1958 Research programs on liver replacement at Northwestern and Harvard
- 1963 First liver transplant (Univ. of CO)
- 1967 First long survival
- 1979 Cyclosporine
- 1987 Univ. of WI solution for improved organ preservation
- 1989 FK 506
- 1999 Living donor liver transplantation

Evolution of liver transplantation in USA

*NEJM* 2002; 346: 1074-1082
Waiting List

Based on OPTN data accessed 7/3/2013

Indications for Liver Transplantation

- Chronic noncholestatic liver disorders
- Chronic hepatitis C
- Chronic hepatitis B
- Autoimmune hepatitis
- Alcoholic liver disease
- Cholestatic liver disorders
- Primary biliary cirrhosis
- Primary sclerosing cholangitis
- Biliary atresia
- Alagille syndrome
- Nonsyndromic paucity of the intrahepatic bile ducts
- Cystic fibrosis
- Progressive familial intrahepatic cholestasis
- Metabolic disorders causing cirrhosis
- Alpha-1-antitrypsin deficiency
- Wilson disease
- Nonalcoholic steatohepatitis and cryptogenic cirrhosis
- Hereditary hemochromatosis
- Tyrosinemia
- Glycogen storage disease type IV
- Neonatal hemochromatosis
- Metabolic disorders causing severe extrahepatic morbidity
- Amyloidosis
- Hyperoxaluria
- Urea cycle defects
- Disorders of branch chain amino acids
- Primary malignancies of the liver
- Hepatocellular carcinoma
- Hepatoblastoma
- Fibrolamellar hepatocellular carcinoma
- Hemangioendothelioma
- Fulminant hepatic failure
- Miscellaneous conditions
- Budd-Chiari syndrome
- Metastatic neuroendocrine tumors
- Polycystic disease
- Retransplantation

Guidelines for Organ Allocation

- Organs should be allocated to transplant candidates in the order of medical urgency.
- The role of waiting times in determining allocation order should be minimized.
- Every attempt should be made to promote efficient use of donor organs.

Figure 1: UNOS regional Map

- Median days TND – No HCV recurrence (n=28): 95
- HCV recurrence (n=10): 5.5 (P <0.001)

• Sofosbuvir + RBV was generally well tolerated
  - Discontinuations due to adverse events: 3% (none related to sofosbuvir)

What Goals do we aim to achieve with immunosuppression after transplantation?

- Control of the immune response:
  - prevent acute rejection
  - minimize chronic rejection
  - prevent autoimmune disease recurrence

Relative Mortality Rates (Transplant vs Waitlist) By MELD (2-Year Follow-up)

PRACTICE GUIDELINE
Long-Term Management of the Successful Adult Liver Transplant: 2012 Practice Guideline by AASLD and the American Society of Transplantation

Timeline for the introduction of immunosuppression medications.

**Induction Phase**

- Relatively high dose calcineurin inhibitors.
- High dose corticosteroids with rapid taper.
- Induction biological agents: monoclonal anti-IL2 antibodies, polyclonal antilymphocyte preparations.
- Adjuvant therapy with MMF or everolimus (sirolimus)

**Maintenance Phase**

- Low dose calcineurin inhibitors alone or with:
  - Adjuvant therapy with mycophenolate or low dose everolimus (sirolimus?).
  - Steroids are maintained at very low dose in selected patients only.
What are the Common Adverse Effects of Immunosuppressive Drugs?

- Tacrolimus: nephrotoxicity, neurotoxicity, diabetes.
- Cyclosporine: nephrotoxicity, neurotoxicity, hyperlipidemia, hypertension.
- Everolimus/Sirolimus: cytopenias, hyperlipidemia, wound healing.
- Mycophenolic acid: cytopenias, GI toxicity.
- Steroids: wound healing, diabetes, bone disease, hyperlipidemia, hypertension.

What goals do we aim to achieve with immunosuppression after transplantation?

- Control of the immune response:
  - Avoid excessive immunosuppression (lack of adequate immune function):
    - 1. infection/sepsis/MSOF:
      - a. post-surgical: urine/bile leak – bacterial
      - b. opportunistic infection
        - i. viral: CMV, EBV, polyoma
        - ii. Fungal
    - 2. malignancy
      - a. Lymphoma/PTLD (EBV)
      - b. cutaneous and visceral
    - 3. disease recurrence (HCV, HBV, HCC)

Best ISP regimen s/p OLTx for HCC?

- An immunosuppressant regimen that includes sirolimus (started several weeks after transplantation) should be considered for patients undergoing transplantation for hepatocellular carcinoma (grade 2, level B).
Causes of Allograft Failure

- Primary Nonfunction – slightly more common in Living Donors
- Vascular Complications – 10% of patients
  - Hepatic Artery Thrombosis/Stricture
  - Portal Vein Thrombosis/Stricture
  - Hepatic Vein Thrombosis/Stricture
- Biliary Complications –
  - Donors after Cardiac Death
  - Living Donors
  - Anastomotic vs nonanastomotic strictures

Causes of Allograft Failure - Rejection

- Antibody Mediated Rejection – hours to days
- 10-20% Acute Rejection
  - Risk 1st 3months>1st year>subsequent years
- Chronic Rejection – a primary RF is prior episodes of Acute Rejection.
- Acute vs Chronic –
  - time course
  - pattern of liver enzyme abnormalities
  - response to therapy

Acute Rejection

- Banff Grading System – each factor 1-3 scale
  - Portal Inflammation
  - Bile Duct Inflammation/damage
  - Venous Endothelial Inflammation

Acute Rejection

- More prominent
  - young recipient,
  - “healthier” recipients,
  - HLA-DR mismatch
  - PSC/PBC/AIH
  - long cold ischemia time
  - older donor.
- Late (>1 year) acute rejection – inadequate immunosuppression.

Chronic Rejection

<table>
<thead>
<tr>
<th></th>
<th>Early CR</th>
<th>Late CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small Bile ducts</td>
<td>Duct loss &lt;50% portal triads</td>
<td>Duct loss&gt;50% portal triads</td>
</tr>
<tr>
<td>Terminal hepatic venules/zone 3 hepatocytes</td>
<td>Zone 3 necrosis/inflammation</td>
<td>Focal obliteration</td>
</tr>
<tr>
<td></td>
<td>Mild perivenular fibrosis</td>
<td>Severe fibrosis – central-central bridging fibrosis</td>
</tr>
<tr>
<td>Portal tract hepatic arterioles</td>
<td>loss &lt;25% portal triads</td>
<td>loss &gt;25% portal triads</td>
</tr>
</tbody>
</table>


- Do you ever discontinue ISP?

9. Although the long-term withdrawal of all immunosuppression can be achieved in a small number of patients, this should be undertaken only with select recipients and under close supervision (grade 2, level C).
Success of Liver Transplantation

- 90+% surgical success
- Minimal late loss to rejection
- Hepatitis C only MAJOR threat of recurrent disease (WAS !!!!)
- No intrinsic attrition rate (unlike kidneys)

Recipient Population

- Average age 47 years.
- Typically non-smoking, non-drinking.
- Increasingly expecting near normal life-expectancy rather than a few bonus years.
- Planning life and family decisions on the expectation of longevity.

Threats to Health and Longevity

- Recurrence
- Malignant disease
- Renal failure
- Cardiovascular disease
- Metabolic disease
- Obesity
- Bone disease

Graft Survival by Pretransplantation Diagnosis

Event-Free Survival (%) vs Years From Transplant Date

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Event-Free Rate (%)</th>
<th>No. at Risk</th>
<th>Cumulative No. of Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B</td>
<td>100.0%</td>
<td>85.8%</td>
<td>82.6%</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>100.0%</td>
<td>85.8%</td>
<td>80.4%</td>
</tr>
<tr>
<td>Other diagnoses</td>
<td>100.0%</td>
<td>86.0%</td>
<td>82.1%</td>
</tr>
</tbody>
</table>

*Hepatitis B vs hepatitis C, P = 0.1148; hepatitis C vs other diagnosis, P = 0.0043; hepatitis B vs other diagnosis, P = 0.9206.
• Shoes, socks, long-sleeve shirts, and long pants should be worn for activities that will involve soil exposure and tick exposure and also to avoid unnecessary sun exposure (grade 1, level A).

• The rate of progression of fibrosis is 3–6 times faster in transplant recipients.

• The median time to the development of bridging fibrosis or cirrhosis is 6 years.

• The rate of progression is related to the amount of inflammation present on the 1-year post-transplant liver biopsy.

Natural History of HCV After Liver Transplantation

• Recurs in all patients who are HCV RNA-positive at the time of transplant.

• The level of virus is higher than before transplant.
  – 1 log increase within 1 month
  – another log within 8-12 weeks
  – 1 log increase during treatment of acute cellular rejection with either steroid boluses or OKT3


Multicenter Experience Using Sofosbuvir + Simeprevir + RBV for HCV Genotype 1 After Liver Transplantation

• Mayo Clinic (3 centers)
  – Histologic evidence of HCV recurrence following liver transplantation (n=109)
  – Sofosbuvir + simeprevir + RBV
• Median follow-up: 23 weeks
• Maintenance immunosuppression (minimal dose adjustment required)
  – Tacrolimus (n=99)
  – Cyclosporine (n=9)
  – Sirolimus (n=1)
• No immunosuppression-related adverse events nor biopsy proven acute rejection
• RBV used in 24 patients, no difference in viral kinetics during treatment


Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Patients (n=109)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (%)</td>
<td>76</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>61</td>
</tr>
<tr>
<td>Non-Caucasian (%)</td>
<td>25</td>
</tr>
<tr>
<td>Median time since liver transplantation (months)</td>
<td>29</td>
</tr>
<tr>
<td>Genotype 1a (%)</td>
<td>62</td>
</tr>
<tr>
<td>IL28B non-CC (%)</td>
<td>71</td>
</tr>
<tr>
<td>Previous HCV treatment failure (%)</td>
<td>68</td>
</tr>
<tr>
<td>PR + PR</td>
<td>12</td>
</tr>
<tr>
<td>Sofosbuvir + PR</td>
<td>1</td>
</tr>
<tr>
<td>METAVIR F3-F4 (%)</td>
<td>20</td>
</tr>
<tr>
<td>Cholestatic recurrence (%)</td>
<td>11</td>
</tr>
<tr>
<td>HCV RNA &gt;800K IU/mL (%)</td>
<td>90</td>
</tr>
<tr>
<td>eGFR &gt;30 mL/min</td>
<td>5</td>
</tr>
</tbody>
</table>

PR: pegIFN + RBV

Patients (n=109)

SVR12 Rates: Sofosbuvir + Simeprevir + RBV for HCV Genotype 1 After Liver Transplantation

### SOLAR:

GT 1 or 4: Post-Transplant F0–F3, CPT A, B, C

- 223 patients randomized 1:1 to 12 or 24 weeks of treatment
- GT 1 or 4 treatment-naive or -experienced post-transplant patients
- ≥ 3 months from liver transplant
- RBV dosing
  - F0–F3/CPT A cirrhosis: weight-based
  - CPT B and C cirrhosis: dose escalation, 600–1200 mg/d

### CORAL-I Study: ABT-450/ritonavir/ombitasvir + Dasabuvir + RBV for HCV Genotype 1 After Liver Transplantation

- Ongoing phase 2 study of 24 weeks of ABT-450/ombitasvir + dasabuvir + RBV
  - HCV genotype 1 (n=34)
  - Liver transplantation due to HCV infection
  - Median time from txp 39.5 mo
  - METAVIR <F2, no prior PI

- SVR 97%
- Relapse 1
- No deaths, graft losses, rejection
- RBV dose reduction: No impact on overall SVR
AASLD/IDSA Guidance on When and In Whom to Treat: HCV Patients Who Have Undergone Liver Transplantation

- Post-transplantation recurrence of HCV may be prevented if SVR is achieved pretransplant
  - Complete HCV viral suppression prior to transplantation prevents recurrent HCV infection of the graft in the majority of cases
  - High pretransplant Child-Pugh or MELD scores are frequently ineligible for early HCV treatment
- Treatment of established HCV infection post-transplantation also yields substantial improvements in patient and graft survival
  - IFN-based triple therapy studies demonstrated feasibility of this approach
  - Newer IFN-free HCV treatment regimens
    - Simplified dosing
    - Better tolerability and fewer drug-drug interactions with immunosuppressive regimens
    - Higher SVR12 rates in multiple genotypes

Malignant Disease

- PTLD
  - Risk correlates with overall intensity of immunosuppression.
  - Estimate of 0.5% per year.
  - Cases seen at 16-23 years.
  - Very poor prognosis unless amenable to surgery and Rx with monoclonal Ab.

Malignant Disease

- 2-3% skin cancers
- Oro-pharyngeal tumours
  - OLTX for alcoholic liver disease
- Increased risk of colonic carcinoma in UC/PSC patients
  - 1% risk per year
  - 21% dysplasia rates by 8 years
  - Annual colonoscopy
Patients with primary sclerosing cholangitis and inflammatory bowel disease or other established risk factors for colorectal cancer should undergo an annual screening colonoscopy with biopsies.

Colectomy, including continence-preserving pouch operations, should be considered when colonic biopsy reveals dysplasia.

(grade 1, level B).

Renal Dysfunction and Failure

- Calcineurin inhibitors (cyclosporine and tacrolimus) associated with renal dysfunction.
- Up to 5% in UK of long-term survivors progressed to dialysis or renal transplantation.
- 40% have serum creatinine >1.2 or creatinine clearance <60 ml/min.
- NEJM study showed ESRD occurred at 1-1.5% per year.

Maintaining Healthy Kidneys

- CNI exposure in first 3 months very important.
- Avoid NSAIDs and other nephrotoxic drugs if possible.
- Screen for early deterioration with creatinine clearance.
- Decrease or eliminate CNI with mycophenolate or sirolimus.

Hypertension

- Implicated drugs include cyclosporine, tacrolimus and corticosteroids.
- US and European trial showed comparable rates in the range of 36-56%.
- Highest rates reported were
  - 82% for cyclosporine
  - 64% for tacrolimus
Hypertension

- The treatment of hypertension should aim for a target goal of 130/80 mm Hg with a combination of lifestyle modifications and pharmacological agents as appropriate (grade 1, level A).
- Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and direct renin inhibitors should be used as first-line antihypertensive therapy in LT recipients with diabetes mellitus, chronic kidney disease, and/or significant proteinuria
  - (grade 1, level A).

Abnormal Glucose Metabolism

- Pretransplant diabetes mellitus.
- Very common early phenomenon.
- Long-term diabetes mellitus
  - increase in treatment intensity
  - *de novo* diabetes mellitus
- Some cases of improvement in DM.
- 4-20% of patients have significant problem.

### Diabetes Mellitus - TMC Study

**First 3 months**

- Tacrolimus 47%
- Cyclosporine 38%
- Insulin 13%
- Drug 4%
- Diet 16%
- Any 51%
- Change from pretransplant diabetic Rx 22%

**4-12 months**

- Tacrolimus 13%
- Cyclosporine 7%
- Insulin 7%
- Drug 2%
- Diet 11%
- Any 19%
- Change from pretransplant diabetic Rx 11%

Lancet 2002; 360: 1119–25
Dyslipidemia

- Hypercholesterolemia 17-43%
- Hypertriglyceridemia 40-59%
- Implicated drugs - cyclosporine, corticosteroids and tacrolimus
- Cyclosporine Vs Tacrolimus
  - 140 to 202 151 to 164 mg/dl (mean)
- Steroid withdrawal 223 to 188 mg/dl
- Pravastatin 251 to 208 mg/dl

Risk Factors for Dyslipidemia

- Cholesterol
  - Pretransplant level
  - Cholestatic liver disease
- Triglycerides
  - Hepatocellular liver disease
  - Renal dysfunction

Tailoring Immunosuppression for Dyslipidemia

- Early steroid withdrawal
- Switch from cyclosporine to tacrolimus - Cambridge study
- Avoid sirolimus

Osteopenia

- 50% of PBC and PSC patients have bone densities below fracture threshold
- 22-38% have atraumatic fractures
- Bone density deteriorates in 90% of patients over first 6 months after transplantation
- Corticosteroids main offending drug
- Cyclosporine and tacrolimus implicated in animal studies only
• 13% fracture rate within 2 years of OLT
• Predisposing factors for Osteoporosis
  – ETOH
  – Tobacco
  – Low Testosterone
  – Physical Inactivity
  – Cholestatic liver disease
  – Indirect hyperbilirubinemia inhibits osteoblast proliferation
• Patients also at risk of Osteonecrosis of Femoral Head

• Treatment of Osteoporosis
  – Calcium 1500mg + vitamin D 800 IU
  – Bisphosphonates well studied
  – Other classes not as well studied but no obvious contraindications
    – Calcitonins, Parathyroid hormone, Selective Estrogen Receptor-Modulators

• For female LT recipients of a child-bearing age, preconception counseling about contraception and the risks and outcomes of pregnancy should start in the pretransplant period and should be reinforced after transplantation (grade 1, level A).

Pregnancy

• Wait 1 year post-OLT
• Most drugs category C
  – (MMF/AZA category D)
• National Transplantation Pregnancy Registry (NTPR) – 2700 pregnancies
  – Live birth rate 70%
  – Congenital anomalies 4-5% vs 3% general population
• Tacrolimus/Low Birth weights range 10-55%
• Tac – lower rates of hypertension/preeclampsia vs CsA
The ideal immunosuppression for pregnancy is tacrolimus monotherapy, which should be maintained at therapeutic levels throughout pregnancy; cyclosporine, azathioprine, and prednisone may also be used if they are necessary (grade 1, level B).

<table>
<thead>
<tr>
<th>Pregnancy (Rejection?)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased serum proteins that lead to increased binding of CNI's and decreased levels</td>
</tr>
<tr>
<td>10% rate of rejection</td>
</tr>
<tr>
<td>Close monitoring of CNI levels throughout pregnancy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Obesity</th>
</tr>
</thead>
<tbody>
<tr>
<td>21.6% of patients developed <em>de novo</em> obesity after liver transplantation.</td>
</tr>
<tr>
<td>Mean body mass index increased from 24.8 kg/m² to 28.1 kg/m² at 2 years.</td>
</tr>
<tr>
<td>Corticosteroids and cyclosporine main responsible drugs.</td>
</tr>
<tr>
<td>Tacrolimus may suppress appetite.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dyslipidemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence 16-43%</td>
</tr>
<tr>
<td>Women, Cholestatic liver disease, DM, Obesity, pretransplant dyslipidemia</td>
</tr>
<tr>
<td>Effects on Lipids:</td>
</tr>
<tr>
<td>CSA, Steroids Sirolimus – greatest effect</td>
</tr>
<tr>
<td>TAC – minor effect</td>
</tr>
</tbody>
</table>
• The measurement of blood lipids after a 14-hour fast is recommended annually for healthy LT recipients.
• An elevated low-density lipoprotein (LDL) cholesterol level >100 mg/dL, with or without hypertriglyceridemia, requires therapy. If therapeutic lifestyle and dietary changes are not enough, statin therapy should be introduced. Suboptimal control with statins can be improved by the addition of ezetimibe (grade 2, level B).
• Isolated hypertriglyceridemia is first treated with omega-3 fatty acids (up to 4 g daily if tolerated). If this is not sufficient for control, gemfibrozil or fenofibrate can be added, although patients must be followed carefully for side effects, especially with the concomitant use of statins and calcineurin inhibitors (grade 2, level C).

• The confirmation of recurrent or de novo nonalcoholic fatty liver disease, the recognition of fibrosis, and the exclusion of alternate causes of elevated liver chemistry tests require liver biopsy (grade 1, level B).

Vaccination
• Vaccines are given prior to transplantation
  – Especially live vaccines
• Restart vaccination 3-6 months after transplantation once baseline immunosuppression is reached – for inactivated vaccines
• Evaluate immunity via assays 4 weeks after administration
  – But serology may not be an accurate measure of immunity during immunosuppression
  – Better markers need to be developed

YOU!
Health care workers and close contacts should be immunized fully
  – The influenza vaccine in particular
  – All are okay except live polio and smallpox

Pets should be fully immunized
Vaccine Particulars

- MMR, Herpes Zoster, Varicella contraindicated because they only come in the live vaccine form
  - Studies in pediatric patients show varicella might be okay post-transplant
    - Not enough evidence to make recommendation
- Pneumococcal vaccine is recommended
  - Pneumovax if older than 5 years
  - Prevnar-13 for children younger than 2 years
- Pneumococcal vaccine
- HPV
  - If not completed before transplant can restart 3-6 months after
- Influenza
  - Yearly
  - Conflicting recommendation between studies and CMS

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Table 1: Recommendations for immunization of adult patients

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Inactivated live attenuated (IM)</th>
<th>Recommended before transplant</th>
<th>Recommended after transplant</th>
<th>Monitor vaccine titers</th>
<th>Quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza (A/B)</td>
<td>LA</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>I</td>
</tr>
<tr>
<td>HSK 2006-02</td>
<td>LA</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>I</td>
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<tr>
<td>Influenza</td>
<td>LA</td>
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<td>Yes</td>
<td>No</td>
<td>I</td>
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<tr>
<td>MMR</td>
<td>LA</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Shigella</td>
<td>LA</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>I</td>
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<tr>
<td>Hepatitis B</td>
<td>LA</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
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</tbody>
</table>

Table 4: Travel vaccine recommendations

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Inactivated live attenuated (IM)</th>
<th>Recommended before transplant</th>
<th>Recommended after transplant</th>
<th>Monitor vaccine titers</th>
<th>Quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yellow fever</td>
<td>LA</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>I</td>
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<tr>
<td>Japanese encephalitis</td>
<td>LA</td>
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<tr>
<td>Salmonella typhi</td>
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<tr>
<td>Typhoid</td>
<td>LA</td>
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<td>No</td>
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<tr>
<td>Typhoid vaccine</td>
<td>LA</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>I</td>
</tr>
<tr>
<td>Yellow fever</td>
<td>LA</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>I</td>
</tr>
</tbody>
</table>

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1. Patients are ideally vaccinated prior to transplantation
2. If not:
   a. Inactivated vaccines are indicated within 3-6 months
   b. Live vaccines are generally contraindicated unless there are extenuating circumstances
3. Healthcare workers and close contacts should be fully immunized
   a. Pets should be fully vaccinated
4. Influenza vaccine is a must for close contacts on a yearly basis
   a. The inactivated vaccine is indicated yearly for patients