Vaccination in Immunosuppressed: Does it work? Is it safe? How to find out

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Past-President, The Transplant Infectious Disease Section, The Transplantation Society
Disclosures: Camille Nelson Kotton M.D.

- **None directly relating to the topic of travel-related vaccination of immunocompromised hosts**
- Consultant:
  - Roche Molecular Systems, Qiagen & Oxford Immunotec (transplant infectious disease diagnostics)
  - Merck (CMV therapeutics)
- Adjudication committees for clinical research: Merck, Astellas (CMV vaccine)
- Research projects with Oxford Immunotec, Qiagen (CMV immunodiagnostics)
- Contributing member for World Health Organization (WHO) Project NOTIFY (Donor Derived Infections)
- Member, Advisory Committee on Blood and Tissue Safety and Availability (ACBTSA), Health and Human Services
- May discuss off-label use: diagnostics, medications, & vaccines
- Spouse has no significant financial disclosures
OUTLINE: Vaccination in Immunosuppressed: Does it work? Is it safe? How to find out

• Define “immunocompromised host”
  – Continuum
• Safety, Immunogenicity and Recommendations
  – Live vaccines
  – Non-live vaccines
• Resources and Tools
Broad Spectrum of Immunocompromise

- Few finite measures of extent of immunosuppression
  - Rapidly evolving fields
  - Individual patient
- Some similar themes
## Estimated Number of Immunocompromised Persons in the US

<table>
<thead>
<tr>
<th>Condition</th>
<th>Estimated # of Persons Living with the Condition in the US</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV infection</td>
<td>1.2 million</td>
</tr>
<tr>
<td>Immune-mediated inflammatory disorders</td>
<td></td>
</tr>
<tr>
<td>RA</td>
<td>1.5 million</td>
</tr>
<tr>
<td>IBD</td>
<td>1.1 million</td>
</tr>
<tr>
<td>SLE</td>
<td>320,000</td>
</tr>
<tr>
<td>Systemic sclerosis</td>
<td>49,000</td>
</tr>
<tr>
<td>Spondyloarthopathies</td>
<td>2.4 million</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>1.0 million</td>
</tr>
<tr>
<td>End-stage renal disease</td>
<td>0.87 million</td>
</tr>
<tr>
<td>Hematologic malignancies including HSCT recipients and candidates</td>
<td>1.0 million</td>
</tr>
<tr>
<td>Solid organ transplant candidates</td>
<td>120,000</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>10 million</strong></td>
</tr>
</tbody>
</table>

2013: 28,954 had organ transplants
>617,000 since 1988

INT 1 Candidates active on the waiting list on December 31
of the year

INT 3 Total transplants, adult and pediatric
# Table 1. Classification of Immunosuppressive Therapies Used in Organ Transplantation or in Phase 2–3 Trials.*

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glucocorticoids</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Small-molecule drugs</strong></td>
<td></td>
</tr>
<tr>
<td>Immunophilin-binding drugs</td>
<td></td>
</tr>
<tr>
<td>Calcineurin inhibitors</td>
<td></td>
</tr>
<tr>
<td>Cyclophilin-binding drugs: cyclosporine,</td>
<td></td>
</tr>
<tr>
<td>ISA(TX)247†</td>
<td></td>
</tr>
<tr>
<td>FKBP12-binding drugs: tacrolimus, modified-</td>
<td></td>
</tr>
<tr>
<td>release tacrolimus‡</td>
<td></td>
</tr>
<tr>
<td>Target-of-rapamycin inhibitors: sirolimus,</td>
<td></td>
</tr>
<tr>
<td>everolimus</td>
<td></td>
</tr>
<tr>
<td>Inhibitors of nucleotide synthesis</td>
<td></td>
</tr>
<tr>
<td>Purine synthesis (IMPDH) inhibitors</td>
<td></td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td></td>
</tr>
<tr>
<td>Enteric-coated mycophenolic acid</td>
<td></td>
</tr>
<tr>
<td>Mizoribine§</td>
<td></td>
</tr>
<tr>
<td>Pyrimidine synthesis (DHODH) inhibitors</td>
<td></td>
</tr>
<tr>
<td>Leflunomide¶</td>
<td></td>
</tr>
<tr>
<td>FK778†</td>
<td></td>
</tr>
<tr>
<td>Antimetabolites: azathioprine</td>
<td></td>
</tr>
<tr>
<td>Sphingosine-1-phosphate–receptor antagonists:</td>
<td></td>
</tr>
<tr>
<td>FTY720‡</td>
<td></td>
</tr>
<tr>
<td><strong>Protein drugs</strong></td>
<td></td>
</tr>
<tr>
<td>Depleting antibodies (against T cells, B cells, or both)</td>
<td></td>
</tr>
<tr>
<td>Polyclonal antibody: horse or rabbit antithymocyte globulin</td>
<td></td>
</tr>
<tr>
<td>Mouse monoclonal anti-CD3 antibody (muromonab-CD3)</td>
<td></td>
</tr>
<tr>
<td>Humanized monoclonal anti-CD52 antibody</td>
<td></td>
</tr>
<tr>
<td>(alemtuzumab)¶</td>
<td></td>
</tr>
<tr>
<td>B-cell–depleting monoclonal anti-CD20 antibody</td>
<td></td>
</tr>
<tr>
<td>(rituximab)¶</td>
<td></td>
</tr>
<tr>
<td>Nondepleting antibodies and fusion proteins</td>
<td></td>
</tr>
<tr>
<td>Humanized or chimeric monoclonal anti-CD25</td>
<td></td>
</tr>
<tr>
<td>antibody (daclizumab, basiliximab)</td>
<td></td>
</tr>
<tr>
<td>Fusion protein with natural binding properties:</td>
<td></td>
</tr>
<tr>
<td>CTLA-4-Ig (LEA29Y†)</td>
<td></td>
</tr>
<tr>
<td>Intravenous immune globulin</td>
<td></td>
</tr>
</tbody>
</table>
Conventional *versus* Biologic Sales, Worldwide

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Conventional vs. biologic sales, worldwide
Percentage of sales attributable to each

**All products**

Conventional drugs

Biologics

**Top 100 sellers**

Conventional drugs

Biologics

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http://www.managedcaremag.com/archives/2013/10/5-years-50-top-selling-drugs-will-be-biologics
### Top 4 Best Selling Biologics of 2013: USA

<table>
<thead>
<tr>
<th>Rank</th>
<th>Biologic</th>
<th>Expression System</th>
<th>Company</th>
<th>2013 Sales</th>
<th>Approved Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Humira (adalimumab)</td>
<td>CHO</td>
<td>AbbVie</td>
<td>10.659 billion</td>
<td>Moderate to severe rheumatoid arthritis, moderate to severe chronic plaque psoriasis, moderate to severe Crohn’s disease; moderate to severe ulcerative colitis, ankylosing spondylitis, psoriatic arthritis, moderate to severe polyarticular juvenile idiopathic arthritis</td>
</tr>
<tr>
<td>2</td>
<td>Remicade (infliximab)</td>
<td>Murine Myeloma</td>
<td>Johnson &amp; Johnson and Merck &amp; Co.</td>
<td>8.944 billion</td>
<td>Moderately to severely active rheumatoid arthritis in adults, in combination with methotrexate; Crohn’s Disease in children 6 years and older, and adults who have not responded well to other medicines; rheumatoid arthritis; ankylosing spondylitis; psoriatic arthritis; chronic, severe, extensive, and/or disabling plaque psoriasis in adults; moderately to severely active ulcerative colitis in children 6 years and older and adults that have not responded well to other medicines</td>
</tr>
<tr>
<td>3</td>
<td>Rituxan (rituximab, MabThera)</td>
<td>CHO</td>
<td>Roche and Biogen Idec</td>
<td>8.920 billion</td>
<td>Non-Hodgkin’s lymphoma, chronic lymphocytic leukemia, and rheumatoid arthritis</td>
</tr>
<tr>
<td>4</td>
<td>Enbrel (etanercept)</td>
<td>CHO</td>
<td>Amgen and Pfizer</td>
<td>8.325 billion</td>
<td>Moderate to severe plaque psoriasis, psoriatic arthritis, and moderate to severe rheumatoid arthritis</td>
</tr>
</tbody>
</table>

Moderate to Severe Chronic Plaque Psoriasis

Clearer skin is possible.

In clinical trials, 7 out of 10 adults with moderate to severe chronic plaque psoriasis saw 75% skin clearance, and the majority of people were clear or almost clear in just 4 months. Your results may vary.

Who is HUMIRA for?

HUMIRA is a prescription medicine used to treat adults with moderate to severe chronic plaque psoriasis who are ready for systemic therapy or phototherapy, and are under the care of a doctor who will decide if other systemic therapies are appropriate.

Important Safety Information

What is the most important information I should know about HUMIRA?

- Serious infections. HUMIRA can lower your ability to fight infections. Serious infections have happened in people taking HUMIRA. These serious infections include tuberculosis (TB) and infections caused by viruses, fungi, or bacteria that have spread throughout the body. Some people have died from these infections.
- You should not start HUMIRA if you have any kind of infection unless your doctor says it is okay.
- Some people have had these serious infections:
  - TB, including active or latent TB lung disease
  - Mycobacterium avium complex (MAC)
  - Malaria
  -Histoplasmosis
  -Coccidiomycosis
  -Pneumocystis jirovecii pneumonia
  -Other fungal infections (e.g., Aspergillus)
  -Candidiasis
  -Salmonella
  -Escherichia coli
  -Campylobacter
  -Clostridium difficile colitis
  -Other opportunistic infections

- Cancer. For children and adults taking TNF blockers, including HUMIRA, the chance of getting lymphoma or other cancers may increase. There have been cases of unusual cancers in children, teenagers, and young adults using TNF blockers. Some people have developed a new type of cancer called lymphoproliferative T-cell lymphoma. This type of cancer often results in death. If you are using TNF blockers, including HUMIRA, your chance of getting two types of skin cancer (basal cell and squamous cell) may increase. These types are usually not life-threatening if treated. Tell your doctor if you have a bump or open sore that doesn’t heal.
- Tell your doctor about all of your health conditions, including if you:
  - Think you have an infection or are being treated for infection. You should not start HUMIRA if you have any kind of infection unless your doctor says it is okay.
  - Have symptoms of an infection, such as fever, chills, headache, or muscle aches
  - Have symptoms of TB, including cough, shortness of breath, weight loss, night sweats, or fever
  - Have symptoms of a fungal infection, such as skin rash, diaper rash, or vaginal yeast infection
  - Have symptoms of a viral infection, such as fever, sore throat, or body aches
  - Have had hepatitis B
  - Are scheduled for major surgery
  - Have or have had cancer
  - Have numbness or tingling or a nervous system disease, such as multiple sclerosis or Guillain-Barré syndrome
  - Have or had heart failure
  - Have recently received or are scheduled to receive a vaccine. HUMIRA patients may receive vaccines, except for live vaccines
  - Are allergic to rubber, latex, or any HUMIRA ingredients

- Allergic reactions.
- Nervous system problems.
- Blood problems.
- Heart failure (new or worsening)
- Immune reactions including a lupus-like syndrome.
- Liver problems.
- Pregnancy (may be harmful to the fetus).
- Breast-feeding

Call your doctor right away if you have an infection or any symptoms of an infection while on HUMIRA.

HUMIRA can cause other serious side effects, including:
- Hepatitis & infection in carriers of the virus.
- You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

You may not be able to afford your medication. Contact your local pharmacy or our customer services department at 1-800-4HUMIRA (1-800-446-8632).

HUMIRA is the #1 Prescribed Biologic Medication by Dermatologists.

HUMIRA is used to treat adults with moderate to severe chronic plaque psoriasis who are ready for systemic therapy or phototherapy, and are under the care of a doctor who will decide if other systemic therapies are appropriate.

Take a moment to learn more at HUMIRA.com or call 1.800.4HUMIRA.

Ask a dermatologist if HUMIRA is right for you.

HUMIRA adalimumab
The More Immunocompromised Host

- Hematopoietic stem cell transplant (HSCT) < 2 years
  - ↑ if graft versus host disease
- Solid organ transplant (SOT) < 1 year
  - ↑ if rejection
- AIDS with low CD4 counts (esp CD4 <200)
- Active leukemia or lymphoma, generalized malignancy, aplastic anemia, recent radiation tx
- Congenital immunodeficiency
- Immunosuppressive medications**
- Chronic hepatic or renal disease, diabetes
- Autoimmune diseases

The Less Immunocompromised Host

- Chemotherapy for leukemia/lymphoma or cancer more than 3 months earlier with malignancy in remission
- HIV patients with >500 CD4 lymphocytes
- HSCT recipients > 2 years post-transplant, no immunosuppressive drugs, no graft versus host disease
- Asplenia
- Nutritional deficiencies
- Steroid inhalers, topical steroids, intra-articular, bursal, or tendon injection of steroids, or were on high-dose steroids over a month ago

Net state of immunosuppression

IMMUNOSUPPRESSION IS ADDITIVE: Consider the Individual Patient

- **Disease state**
  - Advanced organ failure
  - Other organ compromise: kidney, liver, lung, heart

- **Comorbidities**
  - Diabetes, obesity, malnutrition/weight loss, advanced age
  - Viral infections (HIV, CMV, EBV, HCV)
  - Altered microbiome

- **Exogenous immunosuppression**
  - Various mechanisms of action, often used in combination
  - Induction agents @ time of transplant
  - Chronic immunosuppression
  - Treatment of rejection
Aung et al, Travel risk assessment, advice & vaccinations in immunocompromised travellers, Travel Medicine and ID, 2015
### Figure 1. Recommended adult immunization schedule, by vaccine and age group

<table>
<thead>
<tr>
<th>VACCINE</th>
<th>AGE GROUP</th>
<th>19-21 years</th>
<th>22-26 years</th>
<th>27-49 years</th>
<th>50-59 years</th>
<th>60-64 years</th>
<th>≥ 65 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza*</td>
<td></td>
<td>1 dose annually</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetanus, diphtheria, pertussis (Td/Tdap)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Varicella*</td>
<td></td>
<td></td>
<td></td>
<td>2 doses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human papillomavirus (HPV) Female*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3 doses</td>
</tr>
<tr>
<td>Human papillomavirus (HPV) Male*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3 doses</td>
</tr>
<tr>
<td>Zoster*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measles, mumps, rubella (MMR)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 or 2 doses</td>
<td></td>
</tr>
<tr>
<td>Pneumococcal 13-valent conjugate (PCV13)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1-time dose</td>
</tr>
<tr>
<td>Pneumococcal polysaccharide (PPSV23)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 dose</td>
</tr>
<tr>
<td>Meningococcal*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 or more doses</td>
</tr>
<tr>
<td>Hepatitis A*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 doses</td>
</tr>
<tr>
<td>Hepatitis B*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3 doses</td>
</tr>
<tr>
<td>Haemophilus influenzae type b (Hib)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 or 3 doses</td>
</tr>
</tbody>
</table>

For all persons in this category who meet the age requirements and who lack documentation of vaccination or have no evidence of previous infection; zoster vaccine recommended regardless of prior episode of zoster.

Recommended if some other risk factor is present (e.g., on the basis of medical, occupational, lifestyle, or other indication).

No recommendation.
**ADULT VACCINE RECOMMENDATIONS 2015**

![Vaccine Recommendations Table](http://www.cdc.gov/vaccines/schedules/hcp/adult.html)

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http://www.cdc.gov/vaccines/schedules/hcp/adult.html
# Recommendations for Vaccination for Solid Organ Transplant Travelers

## Travel-related

<table>
<thead>
<tr>
<th>Condition</th>
<th>Recommendation</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis A</td>
<td>Recommended when indicated</td>
<td>Recommended per CDC guidelines, minimum age for first dose age 9 months</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Recommended when indicated</td>
<td>Recommended per CDC guidelines, at birth</td>
</tr>
<tr>
<td>Meningococcal conjugate</td>
<td>Recommended when indicated</td>
<td>Recommended per CDC guidelines, minimum age for first dose 9 months</td>
</tr>
<tr>
<td>Inactivated polio (IPV)</td>
<td>Recommended when indicated</td>
<td>Recommended when indicated, minimum age 6 weeks</td>
</tr>
<tr>
<td>Rabies</td>
<td>Recommended when indicated</td>
<td>Recommended when indicated, any age</td>
</tr>
<tr>
<td>Japanese encephalitis</td>
<td>Recommended when indicated</td>
<td>Recommended when indicated; some vaccines not approved for pediatric use and pediatric vaccine not available in United States outside of clinical trials</td>
</tr>
<tr>
<td>Cholera vaccine</td>
<td>Recommended when indicated; not available in USA, available in Canada and elsewhere</td>
<td>Recommended when indicated; not available in USA, available in Canada and elsewhere; approved for use in Canada in 2003 for children 2 years of age and older</td>
</tr>
<tr>
<td>Typhim Vi S. typhi Ty21a</td>
<td>Recommended when indicated</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Oral polio (OPV)</td>
<td>Contraindicated</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Bacille Calmette Guerin</td>
<td>Contraindicated</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Yellow fever</td>
<td>Contraindicated</td>
<td>Contraindicated</td>
</tr>
</tbody>
</table>
Vaccination in immunosuppressed: Does it work? Is it safe?

Vaccine Type: Live Vaccines

Those without specific treatment options:
- Yellow fever
- Measles
- Mumps
- Rubella
- Polio (oral)
- (Rotavirus)

Those with treatment options:
- Salmonella Ty21a
- Varicella
- Zoster
- Influenza
Yellow Fever Zones

(Updated Jan. 23, 2015)

“Travelers with severe immune compromise should be strongly discouraged from travel to destinations that present a true risk for yellow fever (YF).

- They should not undergo YF vaccination, as there is a risk of developing a serious adverse event, such as life-threatening yellow fever vaccine-associated viscerotropic disease.

- If travel to an area where YF vaccine is recommended is unavoidable & the vaccine is not given, these travelers should:
  - be informed of the risk of YF
  - carefully instructed in methods to avoid mosquito bites
  - be provided w/ a vaccination medical waiver.”
Yellow fever vaccine–associated viscerotropic disease (YEL-AVD)

- Uncontrolled replication of vaccine virus
- Multisystem organ dysfunction
- 60% of reported cases are fatal\(^1\)
  - vs severe YF disease 20-50%
- Risk in USA: 0.4 cases per 100,000 doses\(^2\)
  - 1/100,000 in those ≥60yo, 2.3/100,000 ≥70yo\(^3\)
  - Risk in immunocompromised host unknown

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\(^3\) Lindsey NP, Schroeder BA, Miller ER, et al. Adverse event reports following yellow fever vaccination. Vaccine 2008;26:6077–82.
Yellow fever vaccine–associated viscerotropic disease
(Yellow fever virus antigens (red), immunohistochemistry)
MMWR / March 20, 2015

A myocytes in heart
B fibroblasts in vascular wall in lung
C kupffer cell in liver
D fibroblasts, histiocytes skin
“Patients with conditions that the Advisory Committee on Immunization Practices considers precautions to administration of YF vaccine, such as asymptomatic HIV may be offered YF vaccine if travel to YF-endemic areas is unavoidable; recipients should be monitored closely for possible adverse effects.

As vaccine response may be suboptimal, such vaccinees are candidates for serologic testing 1 month after vaccination.

Data from clinical and epidemiologic studies are insufficient at this time to evaluate the actual risk of severe adverse effects associated with YF vaccine among recipients with limited immune deficits.”
• “If international travel requirements, and not true exposure risk, are the only reasons to vaccinate a traveler with asymptomatic HIV-infection or a limited immune deficit, the physician should provide a waiver letter.

• Travelers should be warned that vaccination waiver documents may not be accepted by some countries; if the waiver is rejected, the option of deportation might be preferable to receipt of YF vaccine at the destination.”
MEDICAL CONTRAINDICATION TO VACCINATION
Contre-indication médicale à la vaccination

This is to certify that immunization against
Je soussigné(e) certifie que la vaccination contre

Yellow fever

(Name of disease – Nom de la maladie)

(Name of traveler – Nom du voyageur)

contraindicated because of the following conditions:
contre-indiquée pour les raisons suivantes :

__________________________________ for
__________________________________ pour

__________________________________ is medically
__________________________________ est médicalement

(Signature and address of physician)
(Signature et adresse du médecin)
### Yellow Fever Vaccine & Immunocompromised Hosts: Survey of Case Series and Reports

<table>
<thead>
<tr>
<th>Study</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>da Mota et al, Revista da Sociedade Brasileira de Medicina Tropical 2009 (Brazil)</td>
<td>70 rheumatology patients on treatment, 16 (22%) “minor adverse effect”, none major</td>
</tr>
<tr>
<td>Scheinberg et al, Arthritis Care &amp; Research, 2010 (outbreak, Brazil)</td>
<td>17 rheumatoid arthritis patients receiving Infliximab/methotrexate therapy, repeat YFV vaccine, all w/o specific symptoms from vaccine</td>
</tr>
<tr>
<td>Azevedo et al, TID 2011 (Brazil)</td>
<td>19 SOT recipients vaccinated, no significant side effects</td>
</tr>
<tr>
<td>Barte et al, Cochrane Database Syst Rev. 2014</td>
<td>484 HIV+ developed significantly lower concentrations of neutralizing antibodies w/in first year after immunization compared to uninfected patients - No study patient with HIV infection suffered serious adverse events</td>
</tr>
</tbody>
</table>
Persistence of Yellow Fever Vaccine-Induced Antibodies After SOT, Wyplosz et al, AJT 2013

- All but 1/53 (98%) had protective titers of antibodies after a median duration of 3 years (range, 0.8-21 years) after transplantation.
- Yellow fever antibodies were still detectable after a median time of 13 years (range: 2–32) post-immunization (vaccine timing known, n=46).
A kidney transplant recipient, on tacrolimus/mycophenolate mofetil/prednisone, sees you in preparation for travel to the Amazon. She had a yellow fever vaccine ~11 years ago. She lost her card. What do you recommend for YF coverage?

A. Give yellow fever vaccine

B. Sign *International Certificate of Vaccination or Prophylaxis*: medical contraindication to vaccination against yellow fever

C. Give gamma globulin

D. Check neutralizing antibodies via plaque reduction neutralization test (PRNT)

E. B+C

F. B+D
A kidney transplant recipient, on tacrolimus/mycophenolate mofetil/prednisone, sees you in preparation for travel to the Amazon. She had a yellow fever vaccine ~11 years ago. What do you recommend for YF coverage?

A. Give yellow fever vaccine

B. Sign International Certificate of Vaccination or Prophylaxis: medical contraindication against yellow fever

C. Give gamma globulin

D. Check neutralizing antibodies via plaque reduction neutralization test (PRNT)

E. B+C

F. B+D

For information about serologic testing, contact state health department or CDC’s Division of Vector-Borne Diseases at 970–221-6400.
Number of Reported Measles Cases with onset date from Oct 2014 to Mar 2015 (6M period)

Data source: surveillance DEF file
Data in HQ as of 4 May 2015

[World map showing the number of reported measles cases from Oct 2014 to Mar 2015 with different color codes for the number of cases and a legend indicating the number of countries reporting different ranges of cases.

http://www.who.int/immunization/monitoring_surveillance/burden/vpd/surveillance_type/active/big_measlesreportedcases6months_PDF.pdf]
Measles and Travel Medicine

- Screen for evidence of protection (via infection or vaccine):
  - Document receipt of infection, vaccination, or check serology*
  - Most born pre-1957 are positive (natural disease)
- Immunocompromised hosts **should not receive the live viral measles or MMR vaccine**
  - Could potentially cause disease (i.e. encephalitis)
- Family members can & should get vaccine
- For non-immune immunocompromised hosts with true/high risk exposure, consider prophylaxis (ASAP, but w/in 3-6 days):
  - Gamma globulin (~8 IM injections, 0.5 mL/kg (maximum 15 mL)
  - IVIG adequate protection (200-400 mg/kg)
  - No antiviral therapy available
A significantly immunocompromised patient is accidentally given MMR vaccine in your clinic for presumed non-immunity (b. 1967) before travel to an endemic region. What should you do?

A. Check MMR titers
B. Consider use of gamma globulin or IVIG (intravenous immune globulin)
C. Discuss stopping/reducing exogenous immunosuppression
D. Consider reporting to Vaccine Adverse Event Reporting System (VAERS)(USA) or similar
E. All of the above
What if this occurred with Yellow Fever Vaccine?

Check titers if repeat vaccination
Consider use of gamma globulin or IVIG (intravenous immune globulin) (content adequate?)
Discuss stopping/reducing exogenous immunosuppression
Consider reporting to Vaccine Adverse Event Reporting System (VAERS)(USA) or similar
Vaccine-Derived Poliomyelitis 12 Years after Infection in Minnesota

“Immunocompromised patients should be aware of the risk of transmission of oral polio vaccine virus by the fecal-oral route in parts of the world where that vaccine is still given.”

CDC Yellow Book 2014, Chapter 8, Immunocompromised Travelers

A 44-year-old woman with long-standing common variable immunodeficiency who was receiving intravenous immune globulin suddenly had paralysis of all four limbs and the respiratory muscles, resulting in death. Type 2 vaccine-derived poliovirus was isolated from stool. The viral capsid protein VP1 region had diverged from the vaccine strain at 12.3% of nucleotide positions, and the two attenuating substitutions had reverted to the wild-type sequence. Infection probably occurred 11.9 years earlier (95% confidence interval [CI], 10.9 to 13.2), when her child received the oral poliovirus vaccine. No secondary cases were identified among close contacts or 2038 screened health care workers. Patients with common variable immunodeficiency can be chronically infected with poliovirus, and poliomyelitis can develop despite treatment with intravenous immune globulin.
Does vaccination work in immunocompromised? Yes…

- Very limited data on travel-related vaccines
- Titers generally lower
  - Protection studies lacking
- Increased wane of immunity
  - Higher vaccine doses?
  - More frequent boosting?
  - Intradermal? Adjuvants?
- Optimize timing of vaccines
- Some protection is likely better than none
Response to Hepatitis A Vaccination in Immunocompromised Travelers

Hannah M. Garcia Garrido, Rosanne W. Wieten, Martin P. Grobusch, and Abraham Goorhuis
Center of Tropical Medicine and Travel Medicine, Department of Infectious Diseases, Division of Internal Medicine, Academic Medical Center, University of Amsterdam, The Netherlands

- 85 immunocompromised patients
  - 65 used immunosuppressive drugs →
  - 13 had received stem cell transplants
  - 7 were infected with HIV
- After 1-2 vaccinations, 65 of 85 (76.5%) developed + antibody
- Review: 11 relevant studies
  - Negative impact serologic response rates:
    - high doses of immunosuppressive drugs
    - fewer hepatitis A vaccinations
    - short interval between vaccination and antibody measurement
## Recent Studies of Hepatitis A Vaccine in Immunocompromised

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Design</th>
<th>Patients, No.</th>
<th>Underlying Patient Condition</th>
<th>Drug Regimen&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Primary Outcome</th>
<th>Vaccine-Titer Interval</th>
<th>Protection Rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dumot et al [30]</td>
<td>1999</td>
<td>Clinical trial</td>
<td>8</td>
<td>LTX</td>
<td>Cyclosporine A/tacrolimus/prednisolone</td>
<td>Seroprotection&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2 mo</td>
<td>0</td>
</tr>
<tr>
<td>Stark et al [31]</td>
<td>1999</td>
<td>Clinical trial</td>
<td>39 LTX, 29 RTX</td>
<td>LTX and RTX</td>
<td>LTX: cyclosporine A/tacrolimus; RTX: prednisolone + cyclosporine A +/azathioprine</td>
<td>Seroprotection&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1 mo</td>
<td>LTX: 41; RTX: 24; Controls: 90</td>
</tr>
<tr>
<td>Günther et al [32]&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2001</td>
<td>Clinical trial</td>
<td>27 LTX, 23 RTX</td>
<td>LTX and RTX</td>
<td>LTX: cyclosporine A/tacrolimus; RTX: prednisolone + cyclosporine A +/azathioprine</td>
<td>Duration of protection&lt;sup&gt;d&lt;/sup&gt;</td>
<td>2 y</td>
<td>NR</td>
</tr>
<tr>
<td>Arslan et al [33]</td>
<td>2001</td>
<td>Clinical trial</td>
<td>37 45 (matched)</td>
<td>LTX</td>
<td>Prednisolone + cyclosporine A +/azathioprine</td>
<td>Seroprotection</td>
<td>1st dose: 1 and 6 mo 2nd dose: 1 mo</td>
<td>1 mo: 8; 6 mo: 19</td>
</tr>
<tr>
<td>Radzikowski et al [34]</td>
<td>2011</td>
<td>Clinical trial</td>
<td>66 68</td>
<td>Pediatric IBD</td>
<td>A/6-MP +/prednisolone</td>
<td>Seroprotection</td>
<td>3 mo</td>
<td>Patients: 39; Controls: 64</td>
</tr>
<tr>
<td>Moses et al [35]</td>
<td>2011</td>
<td>Clinical trial</td>
<td>12</td>
<td>Pediatric IBD</td>
<td>Anti-TNF-α</td>
<td>Seroprotection&lt;sup&gt;e&lt;/sup&gt;</td>
<td>1 mo</td>
<td>NR</td>
</tr>
<tr>
<td>Urgenci et al [36]</td>
<td>2013</td>
<td>Clinical trial</td>
<td>23 35</td>
<td>Pediatric IBD</td>
<td>Mesalazine +/prednisolone</td>
<td>Seroprotection&lt;sup&gt;e&lt;/sup&gt;</td>
<td>1 mo</td>
<td>NR</td>
</tr>
<tr>
<td>van den Bijlaardt et al [37]</td>
<td>2013</td>
<td>Retrospective study</td>
<td>173</td>
<td>Underlying disease NR</td>
<td>Anti-TNF-α/DMARDs/other</td>
<td>Seroprotection&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Mean 73 wk (range, 19–430 wk)</td>
<td>Overall: 60</td>
</tr>
<tr>
<td>Park et al [38]</td>
<td>2014</td>
<td>Clinical trial</td>
<td>419</td>
<td>IBD</td>
<td>Anti-TNF-α/azathioprine/6-MP +/prednisolone/none (39 %)</td>
<td>Seroprotection&lt;sup&gt;e&lt;/sup&gt;</td>
<td>1–3 mo</td>
<td>NR</td>
</tr>
<tr>
<td>Askling et al [39]</td>
<td>2014</td>
<td>Clinical trial</td>
<td>53</td>
<td>RA</td>
<td>Anti-TNF-α/anti-TNF-α + MTX/MTX</td>
<td>Seroprotection&lt;sup&gt;f&lt;/sup&gt;</td>
<td>1 and 6 mo</td>
<td>1 mo: 10; 6 mo: 33</td>
</tr>
<tr>
<td>Jeon et al [40]</td>
<td>2014</td>
<td>Clinical trial</td>
<td>52</td>
<td>RTX</td>
<td>Tacrolimus/cyclosporine A +/prednisolone</td>
<td>Seroprotection&lt;sup&gt;e&lt;/sup&gt;</td>
<td>1 mo</td>
<td>NR</td>
</tr>
</tbody>
</table>

Antibody response after 1<sup>st</sup> & 2<sup>nd</sup> vaccination averaged 37% & 82%

Garcia Garrido <i>et al</i>, JID 2015
Checking Serologic Response to Vaccination

- May convey protection
- Could limit total # doses of vaccine

- Adds expense, hassle
- Insufficient time?
- Plan if non-immune?
- Response may be short-lived
- Measure of humoral not cellular immunity
Can vaccines make disease state worse?  

*Primum non nocere*

- No clear evidence for worsening of rheumatologic, dermatologic, GI illness
- Organ transplant – some evidence that influenza vaccine can result in HLA antibody formation
  - Never been shown to increase rates of organ rejection
- Adjuvants: friend > foe?
Family Members & Vaccines

- Avoid live influenza, oral polio*, smallpox*
- Varicella, “The presence of an immunodeficient … family member does not contraindicate vaccine use in other family members.” Red Book, Amer. Academy of Pediatrics
- MMR, zoster, yellow fever acceptable for family members
- Rotavirus?

CDC, Red Book, British Society for Rheum “Vaccinations In The Immunocomp. Person”
**Table 3:** Immunizations for health care workers and other close contacts/household members of transplant candidates/recipients

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Inactivated/ live attenuated (I/LA)</th>
<th>Recommended</th>
<th>Quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza (17–21)</td>
<td>I</td>
<td>Yes</td>
<td>II-2</td>
</tr>
<tr>
<td>Hepatitis B (22–28)</td>
<td>I</td>
<td>Yes</td>
<td>III</td>
</tr>
<tr>
<td>Hepatitis A (29,30)</td>
<td>I</td>
<td>Yes</td>
<td>II-1</td>
</tr>
<tr>
<td><em>H. influenzae</em> (35)</td>
<td>I</td>
<td>Yes</td>
<td>II-2</td>
</tr>
<tr>
<td>Pertussis¹ (Tdap)</td>
<td>I</td>
<td>Yes</td>
<td>II-2</td>
</tr>
<tr>
<td>Varicella (39–42)</td>
<td>LA</td>
<td>Yes</td>
<td>II-2</td>
</tr>
<tr>
<td>Measles (43–46)</td>
<td>LA</td>
<td>Yes</td>
<td>II-2</td>
</tr>
<tr>
<td>Mumps (43,45,46)</td>
<td>LA</td>
<td>Yes</td>
<td>II-2</td>
</tr>
<tr>
<td>Rubella (43,45,46)</td>
<td>LA</td>
<td>Yes</td>
<td>II-2</td>
</tr>
</tbody>
</table>

Danziger-Isakov L, Kumar D, AST ID Community of Practice, Vaccination in solid organ transplantation, Am J Transplant. 2013
Vaccination in immunosuppressed: How to find out

- 2013 IDSA Clinical Practice Guideline for Vaccination of the Immunocompromised Host, CID Dec 2013
- CDC Yellow Book, Chapter 8, Immunocompromised Travelers, CN Kotton & DO Freedman
  - Vaccination in solid organ transplantation, Danziger-Isakov L, Kumar D, AST ID Community of Practice, AJT 2013
- Travel advice for immunocompromised hosts, UpToDate
- Askling & Dalm, The medically immunocompromised adult traveler and pre-travel counseling: status quo 2014, Travel Med ID, 2014
Conclusions: Vaccination in Immunosuppressed: Does it work? Is it safe? How to find out

• Consider “net state of immunosuppression”
  – Consult with treating medical team
  – Consider optimal timing of vaccination and/or travel
• Avoid live vaccines but use non-live (more?) frequently
• Better reporting of vaccine adverse events
• “Cocoon” the immunocompromised patient by surrounding them with well-vaccinated family members
• Discuss, educate, plan
Questions? ckotton@partners.org

Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA
2013 IDSA Clinical Practice Guideline for Vaccination of the Immunocompromised Host

Lorry G. Rubin,1 Myron J. Levin,2 Per Ljungman,3,4 E. Graham Davies,5 Robin Avery,6 Marcie Tomblyn,7 Athos Bousvaros,8 Shireesha Dhanireddy,9 Lillian Sung,10 Harry Keyserling,11 and Insoo Kang12

1Division of Pediatric Infectious Diseases, Steven and Alexandra Cohen Children’s Medical Center of New York of the North Shore-LIJ Health System, New Hyde Park; 2Section of Pediatric Infectious Diseases, University of Colorado Denver Anschutz Medical Campus, Aurora; 3Department of Hematology, Karolinska University Hospital; 4Division of Hematology, Department of Medicine Huddinge, Karolinska Institutet, Stockholm, Sweden; 5Department of Immunology, Great Ormond Street Hospital & Institute of Child Health, London, United Kingdom; 6Division of Infectious Diseases, Johns Hopkins University School of Medicine, Baltimore, Maryland; 7Department of Blood and Marrow Transplant, H. Lee Moffitt Cancer Center and Research Institute, University of South Florida, Tampa; 8Department of Gastroenterology and Nutrition, Children’s Hospital Boston, Massachusetts; 9Department of Allergy and Infectious Diseases, University of Washington, Seattle; 10Division of Hematology-Oncology, Hospital for Sick Children, Toronto, Ontario, Canada; 11Division of Pediatric Infectious Diseases, Emory University School of Medicine, Atlanta, Georgia 12Section of Rheumatology, Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut
Immunization after kidney transplantation—what is necessary and what is safe?

Key points

- In nephrology and transplant medicine, many opportunities for vaccination and protection against infection are missed.
- As immunogenicity is generally greater before transplantation, early in the course of renal disease—or at least before transplantation—is the optimal window of opportunity for vaccination.
- Delaying vaccination for the first 6–12 months after transplantation (or repeating vaccines given early) might result in higher rates of protection; nonetheless, influenza vaccine should be given in season.
- The reported impact of individual immunosuppressive agents on vaccine responses varies between studies; overall, a lower immunosuppressive protocol is more likely to result in clinical protection.
- Although some concern about increased HLA sensitization after vaccination exists, clinical data does not suggest harm; non-live vaccines appear immunogenic, protective and safe.
- Future research is needed into the impact of immunosuppressive protocols on vaccination responses, optimal timing after transplantation, dosing regimens, intradermal administration, clinical protection, use of adjuvants, safety and adverse effects.
Vaccination in Solid Organ Transplantation

L. Danziger-Isakov\textsuperscript{a,*}, D. Kumar\textsuperscript{b} and the AST Infectious Diseases Community of Practice
Table 2: Recommendations for immunization of adult patients

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Inactivated/ live attenuated (I/LA)</th>
<th>Recommended before transplant¹</th>
<th>Recommended after transplant</th>
<th>Monitor vaccine titers</th>
<th>Quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza² (17–21)</td>
<td>I</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>II-2</td>
</tr>
<tr>
<td></td>
<td>LA</td>
<td>See text</td>
<td>No</td>
<td>No</td>
<td>III</td>
</tr>
<tr>
<td>Hepatitis B³ (22,23,26–28)</td>
<td>I</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes (see footnote)</td>
<td>II-2</td>
</tr>
<tr>
<td>Hepatitis A⁴ (29,30)</td>
<td>I</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>II-1</td>
</tr>
<tr>
<td>Tetanus (31–34)</td>
<td>I</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>III</td>
</tr>
<tr>
<td>Pertussis (Tdap)⁵</td>
<td>I</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>III</td>
</tr>
<tr>
<td>Inactivated Polio vaccine</td>
<td>I</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>III</td>
</tr>
<tr>
<td>S. pneumoniae⁶ (13–15,36)</td>
<td>I</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>I</td>
</tr>
<tr>
<td>N. meningitidis⁷ (MCV4)</td>
<td>I</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>III</td>
</tr>
<tr>
<td>Rabies⁸</td>
<td>I</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes (see footnote)</td>
<td>III</td>
</tr>
<tr>
<td>Human papilloma virus (HPV)⁹</td>
<td>I</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>III</td>
</tr>
<tr>
<td>MMR⁹</td>
<td>LA</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>II-2</td>
</tr>
<tr>
<td>Varicella (live-attenuated; Varivax)¹⁰</td>
<td>LA</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>II-2</td>
</tr>
<tr>
<td>Varicella (live-attenuated; Zostavax)¹¹</td>
<td>LA</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>III</td>
</tr>
<tr>
<td>BCG¹²</td>
<td>LA</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>III</td>
</tr>
<tr>
<td>Smallpox¹³ (47)</td>
<td>LA</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>III</td>
</tr>
<tr>
<td>Anthrax</td>
<td>I</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>III</td>
</tr>
</tbody>
</table>

Table 1: Quality of evidence upon which recommendation is based

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Randomized controlled trials</td>
</tr>
<tr>
<td>II-1</td>
<td>Controlled trials without randomization</td>
</tr>
<tr>
<td>II-2</td>
<td>Cohort or case-control analytic studies</td>
</tr>
<tr>
<td>II-3</td>
<td>Multiple time series, dramatic uncontrolled experiments</td>
</tr>
<tr>
<td>III</td>
<td>Opinions of respected authorities, descriptive epidemiology</td>
</tr>
</tbody>
</table>
A 35 yo priest with Goodpasture’s on tx wants to go on a mission to the Brazilian Amazon. With

A. Proceed with yellow fever vaccination
B. Write him a yellow fever waiver letter on your letterhead
C. Have him avoid bites, use DEET, & go to a travel clinic for a yellow fever waiver letter
D. Encourage the use of DEET and hope for the best
Map 5.1 Meningococcal disease in Africa, 1995-1999

Countries reporting more than 15 cases per 100,000 population and an epidemic of meningococcal disease from January 1995 to October 1999

Rabies, countries or areas at risk

- **No risk**: no risk at all.
- **Low risk**: pre-exposure immunization recommended for people likely to have contact with bats.
- **Medium risk**: pre-exposure immunization recommended for travellers and other people for whom contact with bats and other wildlife is likely.
- **High risk**: pre-exposure immunization recommended for travellers and other people for whom contact with domestic animals particularly dogs and other rabies vectors is likely.

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: WHO Control of Neglected Tropical Diseases (NTD)
Map Production: Health Statistics and Information Systems (HSI)
World Health Organization

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http://gamapserver.who.int/mapLibrary/Files/Maps/Global_Rabies_ITHRiskMap.png
Clinical signs and symptoms of infection are protean in the immunocompromised host

Sources of infection:
- Donor
- Recipient
  - Reactivation
  - Colonization
- Nosocomial
- *De novo*
- Geographic
- Emerging
Exposure to broad spectrum antibiotics (treatment & prophylaxis (peritonitis)) increases the risk:

- **Klebsiella, Pseudomonas, & other Gram negatives**
  - Extended spectrum beta-lactamase
  - Carbapenem-resistant and carbapenemase-producing
- **Gram positive**
  - MRSA, VISA (vanco-intermediate *Staph aureus*)
  - VRE
- **Candida**
  - Fluconazole-resistance strains more likely (*C. glabrata*, etc)
Considerations: First Aid Kit Travelling Immunocompromised Patients

Medications

- **Destination-related, if applicable:**
  - Antimalarial medications
  - Medication to prevent high-altitude illness

- **Pain or fever:**
  - Acetaminophen, ASA, or Ibuprofen

- **Stomach upset or diarrhea:**
  - Over-the-counter antidiarrheal medication (loperamide [Imodium] or bismuth subsalicylate [Pepto-Bismol])
  - Antibiotics for self-treatment of moderate to severe diarrhea - obtain prior to leaving home
  - Packets of oral rehydration salts
  - Mild laxative, Antacid

- **Throat and respiratory discomfort:**
  - Antihistamine, decongestant, alone or in combination with antihistamine, cough suppressant, throat lozenges

Basic First Aid

- Disposable gloves (≥2 pairs)
- Adhesive bandages, multiple sizes
- Gauze, adhesive tape, antiseptic
- Elastic bandage wrap for sprains and strains
- Cotton swabs
- Tweezers, scissors
- Antifungal and antibacterial ointments or creams
- Anti-itch gel or cream for insect bites and stings
- Aloe gel for sunburns
- Moleskin or molefoam for blisters - diabetic patients should be especially careful of foot injuries and should check their feet for early signs of irritation

Adapted from Kotton and Hibberd, AJT 2013
Considerations for First Aid Kit for Travelling Immunocompromised Patients

Other Important Items

- Insect repellent (see the Protection against Mosquitoes, Ticks, and Other Insects and Arthropods [http://wwwnc.cdc.gov/travel/yellowbook/2012/chapter-2-the-pre-travel-consultation/protection-against-mosquitoes-ticks-and-other-insects-and-arthropods.htm])
- Sunscreen (≥15 SPF) given higher risk of skin cancer
- Antibacterial hand wipes or an alcohol-based hand cleaner, containing at least 60% alcohol
- Useful items in certain circumstances:
  - Extra pair of contact lenses, prescription glasses, or both
  - Mild sedative (such as zolpidem [Ambien]), other sleep aid, or antianxiety medication
  - Latex condoms