



Chapter 184 – The Solid Organ Transplant Patient

Episode overview:

Core questions:

- 1) List 4 categories of complication in organ transplant
- 2) What are 2 considerations in vaccinating the organ transplant patient?
- 3) List 10 infectious pathogens common in the organ transplant patient?
- 4) What are the 3 categories of graft rejection?
- 5) List 3 categories of immunosuppressants and one example for each
- 6) What are the concerning drug interactions with Cyclosporine, Tacrolimus and Sirolimus?

Key concepts

- The possibility of organ rejection, infection, or drug toxicity should be considered in all organ transplant patients who present to the ED, because the presentations can be subtle.
- Anatomic issues related to solid organ transplantation are specific to the organ transplanted and time since transplantation but generally involve thrombosis, stricture, or breakdown and leakage of the anastomoses.
- Timing since surgery, state of immunosuppression, exposures and risk factors, and graft function should be taken into account at each ED evaluation.
- Differentiation of infection and rejection is often difficult in the ED. Determination is often made only after biopsy of the transplanted organ or positive culture results are identified.
- Infections that occur 1 to 6 months after transplantation are generally immunomodulating viral infections, such as with CMV, or opportunistic infections.
- A patient's inability to take oral immunosuppressants for even a single day should be considered an emergency condition.
- When prescribing new drugs, care should be taken to avoid drug interactions and toxicity of immunosuppressants.

Rosen's In Perspective

Transplants are on the up & up, from community shops to big referral centres, you'll be seeing more and more of them

- Transplanted organs have surgical anastomoses to a variety of structures, including vessels, bronchi, ureters, intestines, and even the bladder
 - They are devoid of their native innervations and thus pain is an unreliable sign of underlying disease
 - The normal inflammatory and immunologic responses to infection and malignant disease are impaired
 - Subtle changes in allograft function may be a harbinger of an episode of rejection
 - Transplant organ complications can generally be classified into one of four categories
 - 1) Anatomy
 - 2) Rejection
 - 3) Infection
 - 4) Drug toxicity
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[1] List 4 categories of complication in organ transplant

- 1) Anatomic
 - Vascular, nonvascular anastomoses, and complications related to surgery.
 - E.g., Hepatic artery thrombosis in liver transplant.
- 2) Rejection
 - Hyperacute (days)
 - Acute (months)
 - Chronic (years)
- 3) Infection
 - E.g., CMV (risk 1 - 6 months), see next question
- 4) Drug Toxicity
 - E.g., Drug-drug interactions

[2] What are 2 considerations in vaccinating the organ transplant patient?

Basically...

- 1) No live vaccines
- 2) Realize that they will mount a minimal response to inactivated vaccine

As per UpToDate:

- Many immunocompromised patients are unable to mount protective immune responses, and live vaccines are usually avoided
- Immunizations should be administered to solid organ transplant candidates as early as possible in the transplant evaluation in order to optimize immune responses and provide immunity to pathogens against which there is only a live vaccine (measles, mumps, rubella, varicella, zoster). We recommend waiting a minimum of four weeks between live virus vaccine administration and transplantation.
- Standard age-appropriate vaccines, as well as vaccines indicated for immunocompromised hosts (e.g., pneumococcal vaccines in adults), should be administered two to six months following transplantation, once maintenance immunosuppression levels have been attained.
- In addition, we recommend that solid organ transplant candidates and recipients be vaccinated against pneumococcus with both the pneumococcal conjugate vaccine (PCV13) and the pneumococcal polysaccharide vaccine (PPSV23).
- We recommend not using live vaccines (measles, mumps, rubella, varicella, zoster, intranasal influenza vaccine) in the majority of solid organ transplant recipients (Grade 1C). An exception is varicella-nonimmune pediatric renal or liver transplant recipients who are receiving minimal or no immunosuppression and who have had no recent allograft rejection; such individuals may receive the varicella vaccine.



[3] List 10 infectious pathogens common in the organ transplant patient

Refer to Box 188.1 in Rosen's 9th edition for a complete list of the infectious pathogens common in transplant patients

Early post-transplantation (0-1 months):

- Preexisting in transplant patient
 - o Bacterial colonization (e.g. *Pseudomonas*, *Mycobacterium*)
 - o Viral (e.g. HIV, HBV, HCV, EBV, CMV, HSV, VZV)
 - o Fungal
- Donor-derived
 - o Bacteria from transplant bacteremia, fungal
- Nosocomial
 - o Bacteremia, surgical site infection, ventilator-associated pneumonia, UTIs, *C. difficile*, MRSA, VRE, respiratory viruses, *Legionella* species

Intermediate post-transplantation (1-6 months):

- Viral infections (e.g., CMV, EBV, HBV, HCV, BK virus, respiratory viruses, HSV, VZV)
- Opportunistic infections (e.g. *Listeria*, *Mycobacterium*, *Candida*, *Aspergillus*)

Late post-transplantation (over 6 months):

- Community-acquired pathogens (respiratory viruses, community-acquired pneumonia, UTI)
- Chronic viral infection (CMV, EBV, HBV, HCV, BK virus)
- Opportunistic infections (in patients remaining on high dose immunosuppression)

[4] What are the 3 categories of graft rejection?

"Rejection involves a complex set of T-cell receptor mediated pathways that lead to cytotoxic activity, B-cell memory and antibody formation, and cell death of the transplant allograft. Each transplant patient typically has a lifelong course of a waxing and waning immune response to the allograft, mandating ongoing surveillance of allograft function. Differentiation of infection and rejection is often difficult and the determination is often made only after biopsy of the transplanted organ or positive culture results are identified." – Rosen's

1) HyperAcute

- Occurs with preformed antibodies against major histocompatibility complex (MHC) or ABO blood type antigens
- It is rare with careful donor-recipient matching, and typically occurs in the immediate perioperative period

2) Acute

- Occurs over days to weeks after transplantation
- The patient presents with constitutional symptoms and signs of transplant organ insufficiency
- Expedient laboratory assessment, imaging, and possible allograft biopsy can confirm the diagnosis of rejection
- If immunosuppression is stopped, acute rejection may occur at any time

3) Chronic

- Now referred to as chronic graft dysfunction
- Time course of months to years
- Results in the gradual failure of the transplanted organ over time



- Each organ presents slightly differently:
 - Interstitial fibrosis and tubular atrophy causing dysfunction in kidneys
 - Inflammation causing airway obstruction in lungs
 - Fibrosis of bile ducts, veins, and arteries in liver
 - Arteriosclerosis, or chronic allograft vasculopathy (CAV) in the heart

[5] List 3 categories of immunosuppressants and one example for each

Typical regime = Cyclosporine + Azathioprine (or Mycophenolate) + Prednisone

Refer to Table 188.1 in Rosen's 9th edition for the common immunosuppressant medications and toxicities

3 Categories:

- 1) Calcineurin inhibitors (e.g. Cyclosporine, Tacrolimus)
- 2) Mammalian target of Rapamycin inhibitors (e.g. Sirolimus)
- 3) Antimetabolites (e.g. Azathioprine, Mycophenolate mofetil (MMF))
PLUS, Corticosteroids (e.g. Prednisone)

[6] What are the concerning drug interactions with Cyclosporine, Tacrolimus and Sirolimus?

Refer to Table 188.2 in Rosen's 9th edition for the drug interactions of Cyclosporine, Tacrolimus and Sirolimus

Pharmacokinetic actions (x3) and their *effects* with examples:

- 1) **Induce cytochrome P450 enzymes (*decreased half-life and immunosuppressive effect, potential for acute rejection*)**
E.g., Carbamazepine, Nafcillin, Phenobarbital, Phenytoin, Rifampin
- 2) **Inhibit cytochrome P450 enzymes (*increased half-life and potential drug toxicity or immunosuppression*)**
E.g., Colchicine, Diltiazem, Fluconazole, Fluoroquinolones, Ketoconazole, Macrolide antibiotics, Oral contraceptives, Verapamil
- 3) **Interact at a glomerular or tubular level (*increased nephrotoxicity*)**
E.g., Aminoglycosides, Amphotericin B, Cimetidine, Nonsteroidals, Sulfur