# THE TRANSPLANT PATIENT

## GENERAL APPROACH

- The kidney is the most commonly transplanted organ (58%), followed by liver (21%), heart, lung and pancreas (less commonly combined organ transplants, intestinal transplant)
- There are also HAEMATOPOIETIC STEM CELL TRANSPLANTS (HSCT) for haematological disease
- Most transplant patients require LIFELONG IMMUNOSUPPRESSION
- These patients can present to ED with any number of acute to life-threatening emergencies:
    - Transplant-related infection
    - Medication side effects
    - Rejection
    - Graft-versus host disease
    - Post-operative complications
    - Complications of altered physiology due to the transplanted organ
    - Common medical problems that require specific management due to immunosuppression or altered physiology
    - New malignancy

## EPIDEMIOLOGY:

- THE MOST COMMON DIAGNOSIS IN ALL STUDIES WAS **INFECTION (39%):**
    - Then noninfectious GI/GU pathology
    - Dehydration
    - Electrolyte disturbance
    - Cardiopulmonary pathology or injury
    - Rejection (6%)
- Acute GVHD occurs in 20-80% of patients post-HSCT, dpending on degree of MHC mismatch and rarely occurs post-solid organ transplant

## HISTORY AND EXAMINATION:

**Table 295-1 Key Historical Elements Specific to Transplant Patients**

| Historical Item | Significance |
|---|---|
| Recent temperature increase or decrease from baseline | Potential clue to onset of infection or, rarely, rejection. |
| Changes from baseline function | Decreased urine may signify rejection in renal transplant patients. |
| | Decreased exercise tolerance may signify rejection in heart transplant patients. |
| | Change in skin color (jaundice specifically) may signify rejection in liver transplant patients or graft-versus-host disease. |
| Date of transplant surgery | The date from transplant helps to predict typical infections and types of post-transplant complications (i.e., graft-versus-host disease occurs). |
| Graft source for solid-organ transplant special features of graft if any, prior infections; donor living related vs. cadaveric | These details predict the potential for certain infections and rejection. |
| Graft source for hematopoietic stem cell transplant: autologous, degree of match, related donor | These details predict the potential graft-versus-host disease. |
| Rejection history | May predict current rejection if similar presentation and difficulty in controlling a current episode of rejection. |
| Recent changes in dosages of antirejection and other medications | Although a planned part of transplant management, rejection is very common when immunosuppression doses are reduced. |
| History of immunizations, chronic infections (CMV, Epstein-Barr virus, hepatitis B and C, other viruses) | Immunizations make targeted infections less likely (but not impossible), and history of chronic infections increase the chances that current presentation is an exacerbation. |
| Recent exposure to patients with infections (chickenpox, CMV, tuberculosis, or persons recently vaccinated for smallpox) | Increases the chance of current infection. |
| Recent history of compliance with immunosuppressive medications. | Noncompliance increases chance of rejection. |
| Recent travel, exposure to persons arriving from countries with endemic infections, exposure to potential foodborne illness or insect vectors | Exposure may predict unusual infections not commonly considered. |
| Complete list of all medications, including nontransplant related, herbal supplements, and over the counter | Complex drug interactions are common causes of symptoms in transplant patients. |
| Baseline: blood pressure, body weight, serum creatinine (for renal transplants), and expected levels of immunosuppressive medications is known | Changes in these parameters may predict rejection or acute illness. |

| Table 295-2 Physical Examination in Transplant Patients | |
|---|---|
| **Examination** | **Comments** |
| Volume status | Often, invasive hemodynamic monitoring (pulmonary artery catheterization) is the only reliable means of determining volume status in transplant patients, but is reserved for critically ill patients in the ED. As tolerated, check orthostatic blood pressure and pulse. |
| Head, ears, eyes, nose, and throat | Periorbital edema (glomerulonephritis), retina (CMV or toxoplasmic chorioretinitis, *Listeria* endophthalmitis), sinuses (*Staphylococcus aureus*, mucormycosis, and invasive fungal disease), mouth (*Candida*, HSV), neck (meningismus, retropharyngeal abscess), lymphadenopathy (CMV, EBV, hepatitis). |
| Lungs | Pneumonia is a common source of infections in transplant patients. *Streptococcus pneumoniae* and other community-acquired agents are still common sources, but opportunistic infections, such as *Pneumocystis jiroveci* pneumonia, *Aspergillus*, tuberculosis, coccidioidomycosis, and viral pneumonias should be suspected. Noninfectious pulmonary infiltrates may also cause dyspnea. |
| Heart | Pericardial friction rubs as a complication of uremia and a wide range of viral infections. |
| Abdomen | Peritonitis without a defined source is one of the most common sites for infection in transplant patients. Right upper quadrant tenderness associated with hepatitis B and C, CMV, and EBV. Varicella-zoster virus causes pancreatitis. If left in place, peritoneal dialysis catheters can be sources of infection. |
| Flank and suprapubic area | The urinary tract was the most common site of infection identified in a study of 352 ED visits by patients after solid-organ transplant.[8] |
| Graft | Renal graft usually placed in abdominal flap; inspection (look for signs of wound infection), palpation (graft tenderness and swelling are often seen in acute rejection, outflow obstruction, and pyelonephritis), and auscultation (bruits suggest renal artery stenosis and AV malformation, or AV fistula). Deep tenderness over liver graft could indicate abscess. |
| Rectal | Perirectal abscess is a common, yet often overlooked, source of infection in transplant patients. |
| Extremities | Access sites for hemodialysis can be sources of infection. Peripheral edema in the transplant patient can represent a number of different etiologies: recurrent versus de novo glomerulonephritis, renal graft failure, liver graft failure, cirrhosis, nephrotic syndrome (from native kidneys), renal vein thrombosis, malnutrition, hypoalbuminemia and heart failure. |
| Skin | Rashes are commonly seen in graft-versus-host disease, viral syndromes (hepatitis B and EBV), cellulitis from indwelling catheter sites, nocardial cutaneous lesions. |
| Mental status/neurologic examination | Cyclosporine/tacrolimus neurotoxicity, steroid psychosis, HSV encephalitis, *Listeria* meningitis/encephalitis, cryptococcal meningitis. |

## DIFFERENTIAL DIAGNOSTIC CONSIDERATIONS AND THEIR MANAGEMENT:

- Solid organ rejection usually involves an immune-mediated inflammatory reaction against the transplanted organ
- Similarly, GVHD is an immune-mediated inflammatory attack against the transplant-recipient body tissues that occurs following HSCT (rarely after solid organ transplant)
- BOTH OF THESE IMMUNE-MEDIATIED INFLAMMATORY REACTIONS CAN RESEMBLE INFECTION (they present with fever and many symptoms/signs/lab anomalies/radiographic findings consistent with infection)
- With liver transplants, the only infeciotn that is likely to resemble rejection is hepatitis C
- In general, solid-organ rejection and exacerbation of GVHD are BOTH TREATED WITH LARGE DOSES OF CORTICOSTEROIDS, INCREASES IN OTHER IMMUNOSUPPRESSIVE MEDICATIONS AND EMPIRICAL ANTIBITOICS ➔ i.e. treatment for both rejection and infection ➔ involve the transplant team early
- FEVER:
    - Temperature can be at the patient's usual baseline with infection

    - If the temperature is even slightly higher or lower than baseline ➔ raised index of suspicion for infection/inflammation
- PERIPHERAL OEDEMA:
    - Can be multifactorial:
        - Hypoalbuminaemia
        - Drugs ➔ CCB
        - DVT
        - Infection
        - GVHD
    - In renal transplant patients ➔ a URINE LEAK may cause fullness and tenderness around the graft with ipsilateral leg swelling

**TREATMENT OF ACUTE GVHD:**

- High-dose corticosteroids can be life-saving ➔ in acute rejection, GVHD and in those with physiologic stress superimposed on chronic steroid use

**<u>GENERAL CARE OF THE TRANSPLANT PATIENT:</u>**

- MAINTAINING IMMUNOSUPPRESSION:
    - Ask about decreased oral intake and if poor, patient should be hospitalized and immunosuppressive medications administered IV
- PRESCRIBING NEW MEDICATIONS FOR PATIENTS TAKING IMMUNOSUPPRESSANTS:
    - It is crucial that we as ED physicians consult up-to-date resources regarding interactions prior to starting or changing medications
    - The patient's transplant team should also be consulted before new medications are prescribed
- AVOID NSAIDS (including aspirin):
    - Many reasons:
        - Patients with transplants will often have recurrent thrombocytopaenia
        - Renal insufficiency is a common side effect of cyclosporine and other immunosuppresives
        - Unexpected bleeding due to transplant complications or GVHD
- STRESS-DOSE STEROIDS:
    - Patients on maintenance steroid therapy who present with suspicion of infection or other significant physiologic stress may need IV stress doses of corticosteroids
    - THERE ARE SITUATIONS WHERE A PATIENT MAY BENEFIT FROM DECREASED STEROID DOSES:
        - Viral infections
        - Post-transplant lymphoproliferative disease
            - CONSULT TRANSPLANT TEAM

## COMPLICATIONS DUE TO IMMUNOSUPPRESSANT MEDICATIONS:

**Table 295-3 Adverse Reactions to Immunosuppressant Medications**

| Medication | Adverse Reactions |
|---|---|
| Azathioprine | Bone marrow suppression.*<br>GI: cholestatic jaundice, pancreatitis.<br>Skin: alopecia. |
| Basiliximab | Immunosuppression.†<br>GI: constipation, nausea, abdominal pain, vomiting, diarrhea, dyspepsia.<br>Peripheral edema.<br>Metabolic: fever, hyperkalemia, hypokalemia, hyperglycemia, hypercholesterolemia, hypophosphatemia, hyperuricemia.<br>Hypertension. |
| Cisplatin | Bone marrow suppression.*<br>Anaphylacticlike reactions: facial edema, wheezing, tachycardia, and hypotension, often within a few minutes of drug administration. If needed, treat with IV epinephrine, corticosteroids, and/or antihistamines.<br>Eye: optic neuritis, papilledema, and cerebral blindness.<br>Ototoxicity tinnitus and/or high-frequency hearing loss.<br>GI: marked nausea and vomiting occur in almost all patients, hiccups, elevated serum amylase.<br>Hepatotoxicity. Transient elevations of liver enzymes, especially serum glutamic oxaloacetic transaminase and/or bilirubin.<br>Renal tubular damage can cause hypomagnesemia, hypocalcemia, hyponatremia, hypokalemia, and hypophosphatemia.<br>Skin: rash, alopecia. |
| Cyclosporine | CNS: headache, paresthesias, dizziness.<br>CVS: hypertension.<br>Tremor or convulsions—often with hypomagnesemia.<br>Gingival hyperplasia.<br>GI disturbance: anorexia, nausea, dyspepsia.<br>Glucose intolerance: hyperglycemia.<br>Renal: nephrotoxicity, hyperkalemia.<br>Skin: hirsutism.<br>Hyperlipidemia.<br>Bone marrow suppression.*<br>Thrombotic thrombocytopenic purpura. |

| | |
|---|---|
| Daclizumab | Immunosuppression.†<br>CNS: headache, dizziness.<br>Autonomic nervous system: hypertension, hypotension GI: constipation, nausea, diarrhea, vomiting, abdominal distention, abdominal or epigastric pain (sometimes food-related).<br>Extremity edema.<br>Urinary: oliguria, dysuria, renal tubular necrosis.<br>Respiratory: dyspnea, pulmonary edema.<br>Insomnia.<br>Musculoskeletal pain.<br>Tachycardia.<br>Thrombosis and bleeding. |
| Daunorubicin | Bone marrow suppression.*<br>Constitutional: dizziness, fever, rigors.<br>CNS: headache, neuropathy.<br>Cardiotoxicity.<br>Respiratory: cough, dyspnea.<br>GI: diarrhea, constipation, abdominal pain, anorexia, vomiting.<br>Musculoskeletal: back pain, arthralgia.<br>Skin: alopecia.<br>Edema. |
| Doxorubicin | Bone marrow suppression.*<br>Myocardial toxicity, CHF.<br>Skin: alopecia.<br>GI: nausea, vomiting, mucositis (stomatitis and esophagitis), ulceration and necrosis of the colon, especially the cecum with bleeding.<br>Conjunctivitis and lacrimation. |
| Fludarabine | Bone marrow suppression.*<br>Neurologic: objective weakness, agitation, confusion, visual disturbances, peripheral neuropathy.<br>GI: nausea, vomiting, anorexia, diarrhea, stomatitis, bleeding.<br>Edema. |
| Imatinib | Bone marrow suppression.*<br>Neutropenia, thrombocytopenia.<br>Fluid retention: pleural effusion, pericardial effusion, pulmonary edema, ascites.<br>Hepatotoxicity. |

| | |
|---|---|
| Methotrexate | Bone marrow suppression.*<br>Methotrexate elimination is reduced in patients with impaired renal function, ascites, or pleural effusions.<br>CNS: headaches, drowsiness, blurred vision, transient blindness, speech impairment, hemiparesis, paresis and convulsions, leukoencephalopathy, encephalopathy.<br>Cardiovascular: pericarditis, pericardial effusion, hypotension, and thromboembolic events.<br>GI: vomiting, diarrhea, and ulcerative stomatitis require interruption of therapy to prevent hemorrhagic enteritis and intestinal perforation.<br>Hepatotoxicity with fibrosis and cirrhosis.<br>Renal toxicity. |
| Mycophenolate mofetil | Bone marrow suppression.†<br>GI: diarrhea, vomiting, mucosal ulcerations, hemorrhage.<br>CNS: headache.<br>Peripheral edema.<br>Acute or chronic interstitial pneumonitis. |
| Muromonab-CD3 | Immunosuppression.†<br>Constitutional: fever >38°C (100.4°F), chills.<br>CNS: headache.<br>Respiratory: dyspnea.<br>CVS: tachycardia or bradycardia, hypotension or hypertension, dizziness, faintness.<br>GI: nausea, vomiting, abdominal pain.<br>Edema. |
| Prednisone | Immunosuppression.†<br>Cushing syndrome.<br>Glucose intolerance: hyperglycemia.<br>Orthopedic: osteoporosis, tendon rupture, aseptic necrosis.<br>Adrenal suppression.<br>Renal: potassium loss, sodium and fluid retention.<br>CVS: pulmonary edema, CHF, hypertension<br>Myopathy: extreme weakness may lead to deep vein thrombosis of legs.<br>Cataracts. |
| Sirolimus | Bone marrow suppression.*<br>Hyperlipidemia.<br>Diarrhea.<br>Hypokalemia.<br>Interstitial lung disease.<br>Nephrotoxicity. |

| | |
|---|---|
| Tacrolimus | Bone marrow suppression.*<br>Nephrotoxicity and electrolytes: renal insufficiency, hyperkalemia or hypokalemia, hypomagnesemia.<br>Hypertension.<br>CNS: tremor, paresthesias, headache.<br>GI disturbance: nausea, vomiting, diarrhea, abdominal pain, constipation.<br>Glucose intolerance: hyperglycemia.<br>Hyperlipidemia. |

*Abbreviations:* CHF = congestive heart failure; CNS = central nervous system; CVS = cardiovascular system.

**Bone marrow suppression* causes varying degrees of thrombocytopenia, anemia, and immunosuppression.

†*Immunosuppression* means one or more of: neutropenia, lymphopenia, lymphocyte dysfunction, and hypogammaglobulinemia. Increased susceptibility to fungal, viral, and other infections should be considered.

**Table 295-4 Physical Examination Clues to Complications of Medications and Graft-Versus-Host Disease**

| Concern | Signs and Symptoms |
|---|---|
| Edema and other swelling | Assess symmetry, pain, color, temperature, and active range of motion. Suspect infection, orthopedic conditions, deep vein thrombosis (due to immobility). |
| Skin break down | The back, pressure points, heels, elbows, and leg ulcers (due to corticosteroid-induced weakness). |
| Joint range of motion | Shoulders, elbows, fingers, wrists, and knees (may be limited due to steroid-induced weakness or sclerodermatous skin changes). |
| Thoracic constriction | Relatively noncompliant edemalike swelling on the chest wall. If present, ask about associated dyspnea on exertion. |
| Abdominal constriction | Firm skin. History of bloating, gas, constipation, diarrhea, nonspecific pains. |
| Sclerodermatous skin | Sclerodermatous skin changes can affect joint mobility, GI and respiratory function. Note the firmness of edema and skin, especially on the thorax and around joints. A firm, soft leather consistency of swelling, tougher than cardiogenic pitting edema can be a serious problem. Assess for recent-onset dyspnea on exertion. |
| Dehydration | Increased thirst, loss of appetite, chills, fatigue, weakness, skin flushing, dark or decrease volume of urine, dry mouth, tachycardia, weight loss. |
| Electrolyte disturbance | Signs and symptoms of dehydration above, hypotension, headache, bradycardia or tachycardia, irregular heartbeat, tremor, muscle weakness, increased urination, constipation, altered tendon reflexes, mood changes, abdominal pain, weight loss, muscle cramping. |

## MANAGEMENT OF MEDICATIONS COMPLICATIONS:

- Mostly done in follow-up
- Medications changes should be made by, or in consultation with, the patient's transplant team

## INFECTIONS IN THE TRANSPLANT PATIENT:

- Account for a large number of deaths in transplant patients, with many undiagnosed until autopsy
- Viral and bacterial illness may occur concurrently
- Immunosuppression-induced blunting of inflammatory response may MASK THE CLASSIC SIGN, SYMPTOMS AND LABORATORY MARKERS OF INFECTION
- Later in the course of infection, patients may present with more advanced ominous signs such as seizure, obtundation, coma and cardiac arrest

## CLINICAL FEATURES:

- Depends on type of infetion and can be predicted (at least in part) by the time-frame since the transplant

**Table 295-5 Infections in Transplant Patients Stratified by Post-Transplant Period**

| Period Post-Transplant/Conditions | Infection | Comments |
|---|---|---|
| <1 mo: resistant organisms | MRSA.<br>Vancomycin-resistant *Enterococcus faecalis*.<br>*Candida* species (including non-albicans). | Opportunistic infections are generally absent during this period as full effect of immunosuppression not complete. MRSA important in HSCT patients. |
| <1 mo: complications of surgery and hospitalization | Aspiration.<br>Catheter infection.<br>Wound infection.<br>Anastomotic leaks and ischemia.<br>*C. difficile* colitis. | *Clostridium difficile* common during this period. Early graft injuries may abscess. Unexplained early signs of infection such as hepatitis, encephalitis, pneumonitis, or rash may be donor derived. |
| <1 mo: colonization of transplanted organ or HSCT neutropenia | *Aspergillus*.<br>*Pseudomonas*.<br>*Klebsiella*.<br>*Legionella*. | Microbiologic analysis of aspirates or biopsy from surgery essential for therapeutic decisions. |
| <1 mo: HSCT-specific infections | Additional bacterial pathogens: *Streptococcus viridans*, and enterococci.<br>Viral infections include respiratory syncytial virus and HSV. | Neutropenia and mucocutaneous injury increase risk for HSCT patients. Lungs, blood stream, and GI tract most commonly affected sites. |
| 1–6 mo: in patients with *Pneumocystis jiroveci* pneumonia and antiviral (CMV, HBV) prophylaxis | Polyomavirus BK infection, nephropathy.<br>*C. difficile* colitis.<br>HCV infection.<br>Adenovirus infection, influenza.<br>*Cryptococcus neoformans* infection.<br>*Mycobacterium tuberculosis* infection.<br>Anastomotic complications. | Activation of latent infections, relapse, residual, and opportunistic infections occur during this period. Viral pathogens and allograft rejection cause the majority of febrile episodes during this period. Polyomavirus BK, adenovirus infections, and recurrent HCV are becoming more common. |

| | | |
|---|---|---|
| 1–6 mo: in patients without prophylaxis | *Pneumocystis*.<br>Infection with herpesviruses (HSV, varicella-zoster virus, CMV, Epstein-Barr virus).<br>HBV infection.<br>Infection with *Listeria*, *Nocardia*, *Toxoplasma*, *Strongyloides*, *Leishmania*, *Trypanosoma cruzi*. | Discontinuation of prophylaxis at the end of this period may prompt active infection, especially CMV. Graft-versus-host disease and mucocutaneous injury increase risk for HSCT patients. |
| >6 mo: general | Community-acquired pneumonia and urinary tract infections.<br>Infection with *Aspergillus*, atypical molds, mucor species.<br>Infection with *Nocardia*, *Rhodococcus* species. | Community-acquired organisms dominate during this period. Transplant recipients have a persistently increased risk of infection due to community-acquired pathogens. |
| >6 mo: late viral infections | CMV infection (colitis and retinitis).<br>Hepatitis (HBV, HCV).<br>HSV encephalitis.<br>Community-acquired viral infections (severe acute respiratory syndrome, West Nile).<br>JC polyomavirus infection (progressive multifocal leukoencephalopathy).<br>Skin cancer, lymphoma (PTLD) | In some patients, chronic viral infections may cause allograft injury (e.g., cirrhosis from HCV infection in liver-transplant recipients, bronchiolitis obliterans in lung transplant recipients, accelerated vasculopathy in heart transplant recipients with CMV infection) or a malignant condition such as PTLD or skin or anogenital cancers. |

- UTI (43%) and pneumonia (23%) are the two most common infections ➔ all-comers with transplant
    - In heart transplant, UTI uncommon (1%), but pneumonia much more common 24%
        - Majority of these patients in one study had a negative work up
- One study of liver transpaltn patients with serious infections found that FEVER WAS ABSENT IN 51% PATIENTS
    - Consider alternative causes of fever as well ➔ drug reaction, rejection, hypersensitivity reaction, malignancy

**DIAGNOSIS:**

| Table 295-6 Diagnostic Tests to Consider in the Evaluation of Infections in the Transplant Patient | |
|---|---|
| **Test** | **Comments** |
| Complete blood count | Leukocytosis or left shift of the white blood cell count may be blunted by immunosuppressive agents. |
| Renal function tests: blood urea nitrogen, creatinine | Supportive, may help determine dosing of antibiotics. |
| Liver function tests | Liver function tests may show mild transaminase elevations with cytomegalovirus and EBV infections, and much higher elevations with hepatotropic viruses such as hepatitis B and C viruses. |
| C-reactive protein | Significant elevations more likely in infections versus noninfectious infiltrates.[20] |
| Procalcitonin level | Significant elevations more likely in infections versus noninfectious infiltrates.[20] |
| CT of the brain | Focal infections in the brain are much more common in this population, but should be used only as clinically indicated. |
| Cyclosporine or tacrolimus level or other levels of immunosuppressants | These levels may be deliberately low depending on the desired level of immunosuppression. |
| Cultures of mouth, sputum, urine, blood, stool, vascular access, and wound sites | Collect as indicated by history and physical. Urine *Legionella* antigen should be considered before treatment of patients with pneumonia with GI complaints. Bacterial and fungal cultures of blood and urine should be obtained on all patients. |
| Cerebrospinal fluid cultures and antigen tests | Collect as indicated by history and physical. |
| Serology: cytomegalovirus, Epstein-Barr virus, hepatitis, toxoplasmosis, cryptococcosis | Because viral and fungal cultures are not very sensitive, clinicians should rely on their acumen to order organism-specific antigen assays and antibody titers. When contemplating viral or parasitic infections, these tests should be obtained to allow identification of bacterial, fungal, and viral pathogens. |
| Chest radiograph | Infiltrates on chest radiograph may reflect infectious or noninfectious complications of hematopoietic stem cell transplant or organ transplant (Figure 295-1). |
| CT of the chest | Patients with evidence of pulmonary infiltrates on chest x-ray or high-resolution CT, but without productive sputum, may ultimately require bronchoscopy with bronchoalveolar lavage and transbronchial biopsy for definitive diagnosis. |
| CT or US to include the graft | These scans can be used to identify likely abscess formation or possibly anastomotic leaks. |
| Tests after admission | Beyond the scope of this chapter, but may include biopsy of the transplanted organ, bronchial alveolar lavage on bronchoscopy, and focused imaging of suspected sites of infection. |

- A series of serious bacterial infection in liver transplant patients presenting to ED found normal or low WCC in 71%
- Leucopenia with an increase in atypical lymphocytes is commonly seen with viral infections ➔ ESPECIALLY CMV
- Pulmonary infections that are frequently encountered include PNEUMOCYSTIS JIROVECI, NOCARDIA, LEGIONELLA PNEUMOPHILA, ASPERGILLUS ➔ these require special stains and studies for accurate diagnosis

**TREATMENT:**

| Table 295-7 Empiric Antimicrobial Therapy | | |
|---|---|---|
| **Condition** | **Antimicrobial Agent** | **Comments*** |
| All patients | Discuss agent(s) with transplant team. | The transplant team caring for the patient should always be consulted as soon as possible; however, in certain life-threatening situations, empiric therapy may be indicated immediately. |
| Suspected infection site based on history and physical examination | Site-specific agents are preferable if predicted by initial findings, balanced by known pathogens as listed in Table 295-5. | The urgency for treatment should be based on the patient's presenting condition; bacterial infections are the most aggressive organisms requiring coverage, but some fungal infections may yield sepsis. In general, broad coverage for any suspected site infection is recommended initially pending cultures and further workup to define noninfectious causes of fever. |
| Neutropenia in the absence of symptoms suggesting site-specific infection | Third-generation cephalosporin such as ceftazidime or a carbapenem plus coverage for MRSA below. | Multiple alternative agents used, including an aminopenicillin plus a β-lactam inhibitor such as piperacillin-tazobactam, or cefepime. Monotherapy has fewer complications, but concern for MRSA remains high. Addition of antiviral and antifungal agents should be at the discretion of the transplant team. Imipenem may cause seizure activity. |
| Suspected MRSA | Vancomycin. | In the majority of patients, MRSA infection should be seriously considered as a potential cause of infection, pending cultures. Linezolid is an alternative to vancomycin. |

## SPECIFIC INFECTIONS:

### WOUND COMPLICATIONS:

- Post-operative wound infections include:
  - Haematoma
  - Superficial/deep wound dehiscence
  - Perigraft fluid collections
  - Superficial and deep wound infection
  - Cellulitis
  - Lymphocele
  - Wound drainage
- Presentation may be subtle
- Fever, chills, incisional pain, erythema and drainage may not always be present due to immunosuppressive diminution of signs of inflammation
- INFECTION CAN LEAD TO NECROTISIN FASCIITIS
- Serious wound infection may require removal of sutures, packing of the wound, irrigation and long-term antibiotic therapy ➔ TREAT WITHOUT DELAY
- Even for minor wound infection, the patient's transplant team should be consulted concerning immediate treatment

### CENTRAL NERVOUS SYSTEM INFECTION:

- Likely to present differently in transplant patient, more subacute symptoms and signs
- HOWEVER ➔ altered mental state, headache and focal neurological deficit or UNEXPLAINED FEVER should raise suspicion
- MRI IS FIRST-LINE ➔ better for posterior fossa abscess, cerebritis, surrounding oedema, extent of mass effect, associated thrombosis

- CSF examination ➔ LISTERIA MONOCYTOGENES, CRYPTOCOCCUS NEOFORMANS, ASPERGILLUS FUMIGATUS
    - Focal brain infection often caused by Aspergillus, Toxoplasma, Nocardia
- CNS disease is also caused by CMV, HSV 6, West Nile virus and varicella

**INVASIVE PNEUMOCOCCAL INFECTION:**

- Relatively common in lung, kidney and heart transplant patients, despite antibiotic prophylaxis and vaccination
- COINFECTIONS ARE COMMON ➔ CMV, Pseudomonas, micrococcs, Serratia, Aspergillus, Stenotrophomonas
- If found to be HYPOGAMMAGLOBULINAEMIC ➔ replacment may be a helpful addition to the treatment regimen

**GI INFECTIONS:**

- Treatment should be guided by stains, other tests and by transplant team
- Clostridium difficile colitis is common in the early months following HSCT ➔ high volume diarrhoea may persist for weeks and TPN is often required

**PARASITIC INFECTION:**

- PNEUMOCYSTIS JIROVECI (formally PCP) may present by itself or with CMV
    - DIAGNOSIS ➔ may require BRONCHOALVEOLAR LAVAGE (BAL)
    - Early prophylaxis with BACTRIM has greatly reduced the incidence of Pneumocystis infection
- TOXOPLASMA GONDII:
    - May cause a meningoencephalitis or single or multiple mass lesions and may cause fever, mental status changes, focal neurologic signs, seizures or visual changes

**CYTOMEGALOVIRUS:**

- CMV is the most common serious viral after solid-organ transplantation
- ALL TRANSPLANT PATIENTS MUST HAVE CMV-NEGATIVE BLOOD PRODUCTS
- SYSTEMIC EFFECTS:
    - PNEUMONITIS is one of the most serious effects
    - Can produce a mononucleosis-like syndrome → fever, arthralgias, malaise, fatigue, neutropenia, atypical lymphocytes, thrombocytopaenia with MILD TO MODERATE ELEVATION OF TRANSAMINASES
        - Jaundice is rare
    - There can also be gastroenteritis
    - CMV is frequently associated with opportunistic infection due to an ADDITIONAL IMMUNOMODULATORY EFFECT OF ITS OWN → this also creates a PROPENSITY FOR ALLOGRAFT REJECTION (thus consider CMV in organ rejection)
    - Due to its ability to infect endothelial cells, it has been considered to contribute to hepatic artery thrombosis in liver transplant patients
    - CAN ALSO CAUSE CNS DISEASE ➔ ventriculitis and myelitis

- CMV PNEUMONIA:
    - Decreased significantly due to ROUTINE PROPHYLAXIS WITH GANCICLOVIR in high-risk patients in the first 100 days following HSCT and preemptive treatment of patients with subclinical viraemia
    - CMV pneumonia ➔ nonproductive cough, SOB, fever, hypoxia that rapidly progresses to ACUTE RESPIRATORY FAILURE
    - Diffuse interstitial nodules and ground-glass infiltrates on CXR
    - Diagnosis is established by viral inclusion bodies in lung biopsy
    - Treat CMV pneumonia with GANCICLOVIR AND IMMUNOGLOBULINS
    - Ganciclovir is associated with:
        - Neutropenia
        - Nephrotoxicity
        - Seizures
        - Retinal detachment
            - FOSCARNET IS AN ALTERNATIVE (ARF is a problem with this drug)
- CMV CHORIORETINITIS:
    - May present with decreased visual acuity, photophobia, scotomata, floaters, eye redness or pain
    - POOR PROGNOSIS, REPRESENTS PROFOUND IMMUNOSUPPRESSION
    - Rapid transfer to transplant centre or ophthalmologic assessment

**RESPIRATORY SYNCYTIAL VIRUS:**

- Presents with upper respiratory tract symptoms
- ONCE PNEUMONIA DEVELOPS, MORTALITY IS VERY HIGH (approaches 80%!)
- HHV-6 can cause ROSEOLA in kids ➔ can cause pneumonitis, bone marrow suppression and encephalitis in transplant patients

**PARVOVIRUS B19:**

- Red blood cell aplasia due to above infection can occur in those receiving immunosuppressants
- THERE IS NO SPECIFIC ANTIVIRAL MEDICATION
- Treatment includes reduction in immunosuppression and IV immunoglobulin

**VARICELLA ZOSTER VIRUS:**

- Two distinct syndromes:
    - Those with prior exposure (childhood chickenpox) ➔ present with typical reactivation type infection limited to skin eruption
    - Those with no prior exposure ➔ PRIMARY VARICELLA INFECITON, usually contracted when tissue from a seropositive donor is transplanted to a seronegative host

        - Can produce just a simple chickenpox syndrome or can progress to VIRULENT DISEASE ➔ haemorrhagic pneumonia to encephalitis, hepatitis, pancreatitis. HIGH MORTALITY RATE
- ACYCLOVIR, VALACYCLOVIR OR FAMCICLOVIR indicated for both reactivation and primary infection
- IMMUNISATION WITH ATTENUATED VIRUS IS CONTRAINDICATED AFTER TRANSPLANT
- Seronegative patients who are exposed to varicella should receive VARICELLA IMMUNOGLOBULIN ASAP (certainly within 96 hours) as postexposure prophylaxis

**HERPES SIMPLEX VIRUS:**

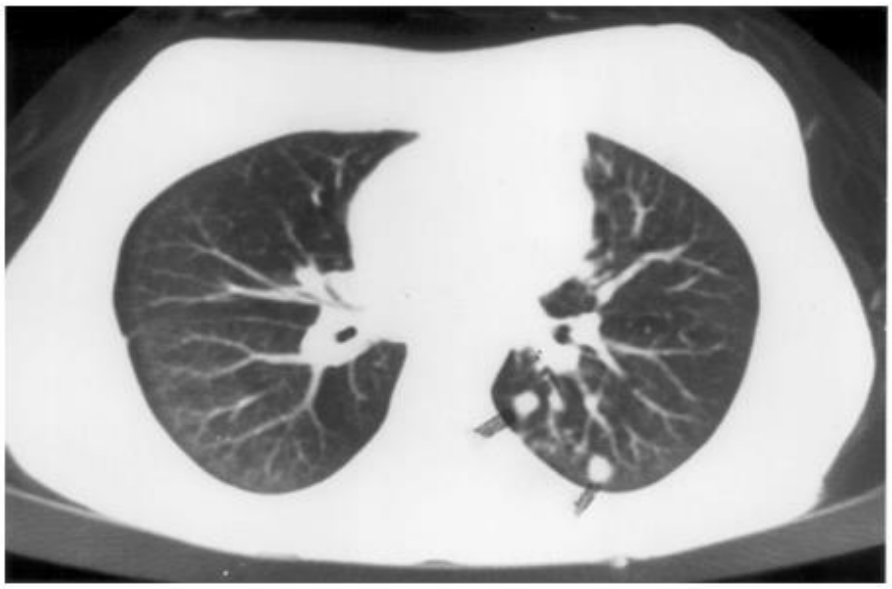
- RELATIVELY COMMON DURING THE FIRST MONTH POST-TRANSPLANT
    - Largely a reactivation disease presenting with typical mucocutaneous ulcerations
    - Oral antivirals sufficient
- PRIMARY DISEASE:
    - Acquired from the donor organ
    - Presents with life-threatening hepatitis, pneumonitis or meningoencephalitis
    - Classic herpes lesions are the EXCEPTION rather than the rule
    - Maintain high index of suspicion and pay attention to timing after transplant
    - IV acyclovir indicated

**HEPATITIS B AND C:**

- May contracted from an infected donor or may reactive with immunosuppression following transplantation
- Seropositive patients frequently progress to active hepatitis, cirrhosis or hepatocellular carcinoma

**ASPERGILLUS:**

- THE MOST LIKELY FUNGAL ORGANISM TO AFFECT THE LUNGS AND PARANASAL SINUSES
- Candida albicans is the most common fungal pathogen overall, but rarely involves the lungs
- ASPERGILLOSIS:
    - Highly invasive
    - Frequently causes pain due to involvement of pleura, diaphragm and pericardium as well as blood vessels
    - Diagnosis is difficult
    - Mortality can be as high as 85%
    - A number of radiographic abnormalities (see below)
    - Radiographic findings ➔ small pulmonary nodules, cavitating lesions, consolidation and pleural effusions, nodular opacities on CT



- In more immunocompetent patients, fungal infection may be more localised, forming an ASPERGILLOMA ➔ surgical removal may be curative

**DISSEMINATED CANDIDIASIS:**

- HIGH MORTALITY
- Albicans is the most frequent species isolated, but NON-ALBICANS SPECIES (e.g. Glabrata) are a special concern as they ARE HIGHLY VIRULENT and associated with treatment failure with standard antifungal agents.
  - Hence obtain species-specific information if fungi are isolated from sterile body-fluids of any transplant patient

**CRYPTOCOCCUS NEOFORMANS:**

- PULMONARY CRYPTOCOCCOSIS ➔ may be asymptomatic or present nonspecifically with a cough, fever or pleural symptoms
- MENINGITIS ➔ common features of infection, especially in solid-organ transplant, but symptoms are frequently SUBTLE
- A positive SERUM CRYPTOCOCCAL ANTIGEN is reliable for the diagnosis of disseminated disease and should prompt an LP to exclude CNS disease
- All CSF specimens from transplant recipients that show abnormal biochemical paramaters or raised leukocytes without adequate explanation should be tested for cryptococcal antigen and cultures for adequate period to encourage isolation
  - INDIA INK

**Induction therapy**:

amphotericin B desoxycholate (adult and child) 0.7 up to 1 mg/kg IV, daily (dosage to be adjusted according to tolerance) for at least 2 weeks [Note 1] [Note 2]

PLUS

flucytosine (adult and child) 25 mg/kg IV or orally, 6-hourly for at least 2 weeks (monitor plasma concentrations, see Monitoring of flucytosine) [Note 3].

**Consolidation therapy**:

fluconazole 800 mg (child: 20 mg/kg up to 800 mg) orally, for the first dose, then 400 to 800 mg (child: 10 mg/kg up to 400 mg) orally, daily for at least 8 weeks of therapy.

**Eradication or maintenance (suppression) therapy**

For ***C. gattii*** infection, if there has been a successful response after 8 weeks of fluconazole at the consolidation dose, change to:

**fluconazole 400 mg (child: 10 mg/kg up to 400 mg) orally, daily.**

For ***C. neoformans*** infection, if there has been a successful response after 8 weeks of fluconazole at the consolidation dose, change to:

**fluconazole 200 mg (child: 5 mg/kg up to 200 mg) orally, daily in HIV-positive patients**
**or fluconazole 400 mg (child: 10 mg/kg up to 400 mg) orally, daily is generally preferred in organ transplant recipients and in immunocompetent patients.**

## TUBERCULOSIS:

- The clinical presentation of TB in transplant patients is HIGHLY VARIABLE
  - Cavitary pulmonary disease
  - Miliary disease
  - Multi-organ involvement
- It occurs in only 5% of transplant patients, but half of these present as disseminated disease!
- Definitive diagnosis is by organism identification and culture form sputum, pleural fluid and BAL, lung or bone marrow biopsy
- Therapeutic options are complicated due to interactions of antituberculous medications with cyclosporine

## WEST NILE VIRUS:

- Produces an encephalitis that is similar to non-transplant patients, but neurologic injury is more severe
- FEVER, NAUSEA/VOMITING, WEAKNESS, DIARRHOEA
- Neurologic signs develop rapidly and may be associated with ACUTE FLACCID PARALYSIS
- CSF ➔ pleocytosis (lymphocytes), West Nile IgM, normal glucose
- Treatment is supportive in addition to manipulation of immunosuppressive medications in conjunction with transplant team

## GRAFT VERSUS HOST DISEASE:

- A major cause of morbidity and mortality affecting approximately 50% of allogeneic HSCT patients
  - Considered acute if it appears up to 100 days post HSCT ➔ prompt recognition and treatment can be life-saving
  - Chronic GVHD is a late complication of allogeneic HSCT, with multisystem alloimmune and autoimmune features that is characterised by immune dysregulation and decreased survival

## ACUTE GVHD:

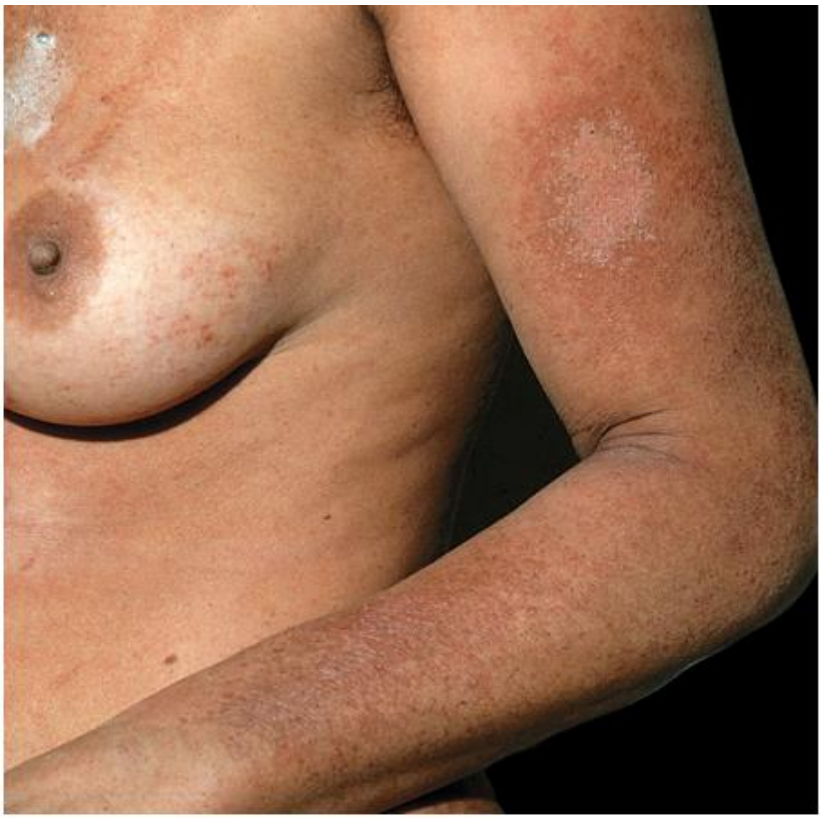
- The incidence ranges from 30-60% following allogeneic HSCT
- If this becomes STEROID REFRACTORY → chances of survival are slim
- In those who recover, chronic GVHD is common

| Table 295-7.2 Conditions Treated with Hematopoietic Stem Cell Transplant Creating Risk for Graft-Versus-Host Disease |
|---|
| Malignancies |
| Leukemia |
| Lymphoproliferative disorders |
| Myeloma |
| Myelodysplastic syndrome |
| Solid tumors |
| Breast cancer |
| Germinal tumors |
| Neuroblastoma |
| Ovarian tumors |
| Nonmalignant hematologic conditions |
| Anemias |
| Aplastic |
| Fanconi anemia |
| Severe sickle cell |
| Congenital erythropoietic porphyria |
| Severe combined immune deficiency |
| T-cell immunodeficiencies |
| Autoimmune diseases |
| Rheumatoid arthritis |
| Systemic lupus erythematosus |
| Multiple sclerosis |
| Systemic sclerosis |
| Metabolic diseases |
| Hurler syndrome |
| Leukodystrophies |
| Gaucher disease |

| Table 295-7.1 Pathophysiology of Graft-Versus-Host Disease and Transfusion-Associated Graft-Versus-Host Disease |
|---|
| Factors required to develop graft-versus-host disease, Billingham conditions. |
| 1. The graft must contain immunologically competent cells. |
| 2. The host (recipient) must possess important transplantation antigens that are lacking in the donor graft. Thus, the host appears foreign to the graft and is therefore capable of stimulating the graft antigenically. |
| 3. The host itself must be incapable of mounting an effective immunologic reaction against the graft, at least for sufficient time for the graft to survive. |
| Clinical factors meeting Billingham conditions in transfusion-associated graft-versus-host disease. |
| Billingham conditions 1 and 2 are usually met in routine blood product transfusions (except for fresh frozen plasma). |
| Billingham condition 3 will be met in patients who are: |
| a) Immunocompetent patients who receive blood products from genetically similar donors (blood relatives). |
| b) Patients with disease-related immunologic deficiencies, such as hematopoietic stem cell transplant patients. |
| c) Solid-organ transplant and other patients who have received purine analogs; the effects of fludarabine and cladribine (2-CdA) persist for 1 y or more. |

- CLINICAL FEATURES:
    - NON-SPECIFIC RASH (most common)
    - Diarrhoea (second-most common)
        - If either of these symptoms present post HSCT, consider acute GVHD
    - CUTANEOUS AND MUCOCUTANEOUS DISEASE:

        - Skin involvement ➔ maculopapular rash that can be pruritic or painful, frequently demonstrating BROWNISH HUE and SCALING



        - Distribution varies greatly but often affects palms and soles initially
        - Mucositis has been reported to occur in 35-70% patients
    - GI DISEASE:
        - Diarrhoea, with or without upper GI symptoms (anorexia, nausea, vomiting) is common
        - The patient may develop painful cramping, ileus and sometimes, LIFE-THREATENING HAEMORRHAGE FROM THE COLON
            - The patient with serious GI haemorrhage in the early post-transplant period may have coagulation deficits, especially thrombocytopaenia
            - Differential for GI bleeding in this setting includes all the usual suspects in addition to acute GVHD and infection (viral, fungal ro bacterial)
            - Gastro will ultimately need to be consulted for endoscopic evaluation and complete diagnosis
- **TREATMENT ➔ PO prednisone or IV methylprednisolone at 1-2mg/kg in consultation with the patients transplant team**
    - If other immunosuppressives have recently been tapered or discontinued, it may be helpful to increase these as well

**TRANSFUSION-ASSOCIATED GVHD:**

- In some patients, TRANSFUSED CELLS ENGRAFT, EXPAND AND CIRCULATE
    - When immunocompetent T-lymphocytes engraft in an immune-suppressed patient, transfusion-associated GVHD may occur and is almost always fatal
    - THIS IS THE RATIONALE BEHIND GIVING IRRADIATED/LEUKODEPLETED BLOOD PRODUCTS TO ALL PATIENTS, BUT PARTICULARLY TO IMMUNOSUPPRESSED PATIENTS
- CLINICAL FEATURES:
    - Fever, skin rash, liver dysfunction and diarrhoea like other forms of GVHD but also has MARROW APLASIA and thus has a more fulminant and rapid course
    - PANCYTOPAENIA DEVELOPS WITHIN 16 DAYS
        - Neutropenia progresses, with death usually due to infections within 3 weeks
        - Mortality is >90% because there is NO EFFECTIVE TREATMENT OTHER THAN PREVENTION
- RISK FACTORS OUTLINED BELOW

| **Table 295-8 Risk Factors for the Development of Transfusion-Associated Graft-Versus-Host Disease** |
|---|
| Significantly increased risk |
| Congenital and acquired immunodeficiency syndromes |
| History of bone marrow (stem cell) transplantation, whether allogeneic or autologous) |
| Transfusions from blood relatives ("directed donation") |
| Intrauterine transfusions |
| Newborn exchange transfusions |
| Transfusions with fresh whole blood |
| Premature infants receiving any sort of transfusion |
| Human leukocyte antigen–matched platelet transfusions |
| Hodgkin disease, even when in remission |
| Leukemia not in remission |
| Patients treated with purine analogs; the effects of fludarabine and cladribine (2-CdA) persist for a year |
| Minimally increased risk |
| Non-Hodgkin lymphoma |
| Acute or chronic leukemia in remission |
| Solid tumors treated with intensive chemotherapy or radiotherapy |
| Exchange transfusions |
| Preterm infants |
| Solid-organ transplant recipients |
| Perceived but no reported increased risk |
| Healthy newborns |
| Patients with acquired immunodeficiency syndrome |

- PREVENTION:
    - Filtration leukoreduction appears insufficient

- CELLULAR BLOOD PRODUCTS SHOULD BE IRRADIATED BEFORE BEING GIVEN to persons who are immunosuppressed or are close relatives of the donor
- FFP does not need to be irradiated but red cells, platelets, GCSF and fresh plasma do!

## THE HAEMATOPOIETIC STEM CELL TRANSPLANT PATIENT:

- HSCT is used to treat haematopoietic malignancies, some solid tumour, severe anaemias and some autoimmune conditions
- HSCT is also used to reconstitute the immune system in immunodeficiency states

## COMPLICATIONS OF HSCT:

**Table 295-9 Time Periods When Hematopoietic Stem Cell Transplant Complications Are Likely to Occur**

| **0-30 d Post-HSCT: The Preengraftment Period of Neutropenia** | |
|---|---|
| **System/Complication** | **Comments** |
| Hyperacute graft-versus-host disease | Severe form of disease |
| Neurologic | Complications of treatment responsible for many symptoms. Aspergillosis is a major cause of focal brain infection. |
| Central nervous system infection | — |
| Metabolic encephalopathy | — |
| Cardiac<br>Congestive heart failure<br>Arrhythmias | Cardiac disease may be preexisting due to chemotherapy treatment pre-transplant. Arrhythmias are due primarily to electrolyte abnormalities and critical illness in the immediate post transplant period. |
| Pulmonary<br>Diffuse alveolar hemorrhage<br>Engraftment syndrome<br>Capillary leak syndrome | Engraftment syndrome presents with fever and pulmonary infiltrates. High mortality rate with diffuse alveolar hemorrhage (Figure 295-1), treatment is supportive. |
| GI/hepatic<br>GI bleeding<br>Enteritis (*C. difficile* dominant)<br>Veno-occlusive disease (liver)<br>Typhlitis | Most enteritis is associated with treatment early on, including *Clostridium difficile*, which may be resistant to vancomycin. Bleeding associated with graft-versus-host disease may respond to corticosteroids. |
| Renal<br>Hemorrhagic cystitis<br>Hyponatremia | Treatment of hemorrhagic cystitis is IV hydration, diuresis, irrigation of the bladder, and use of mesna, a chemoprotectant. |
| Infections (Table 295-5)<br>Bacteria associated with lines, procedure<br>*Candida*<br>*Aspergillus*<br>Respiratory syncytial virus<br>Herpes simplex virus | *Aspergillus* accounts for 25%–50% of pneumonias in allogeneic transplant recipients. Treatment is with voriconazole.[26] |

| 31–100 d Post-HSCT: Early Post-Transplant, Acute Graft-Versus-Host Disease | |
|---|---|
| Neurologic<br>CVA | CVA primarily due to intracranial bleeding. |
| Cardiac<br>Pericardial effusion<br>Endocarditis | Endocarditis is frequently missed. *Staphylococcus aureus* and *Streptococcus viridans* are the most common organisms. |
| Pulmonary<br>Idiopathic pneumonia syndrome<br>Lymphocytic interstitial pneumonia<br>Bronchiolitis obliterans organizing pneumonia<br>Thoracic constriction | Treatment of idiopathic pneumonia syndrome is supportive, covering for any suspected infections. Treatment for bronchiolitis obliterans organizing pneumonia is long-term macrolides. |
| GI/hepatic<br>Viral hepatitis<br>Enteritis (*C. difficile* dominant)<br>Intestinal graft-versus-host disease | Corticosteroids are the drug of choice for intestinal graft-versus-host disease. |
| Renal<br>Cyclosporin toxicity | Dose reduction may help if condition will allow. |
| Infections (Table 295-5)<br>Cytomegalovirus (pneumonia, gastroenteritis and ocular infections)<br>*Pneumocystic jiroveci* pneumonia<br>Adenovirus<br>Herpes zoster virus<br>*Aspergillus* | Cytomegalovirus is the most important viral infection in post-HSCT patients. Treatment is with ganciclovir and foscarnet. |
| Hematologic<br>Thrombotic thrombocytopenic purpura | May be associated with rapid demise. |

| More than 100 d Post-HSCT: Late Post-Transplantation Period | |
|---|---|
| Neurologic<br>Myopathy<br>Neuropathy | Many patients do not respond to commonly used agents. |
| Pulmonary<br>Community-acquired pneumonia<br>Bronchiolitis obliterans<br>Thoracic constriction | Increased risk for community-acquired pneumonia. Intensive therapy for graft-versus-host disease may be needed for thoracic constriction such as photophoresis. |
| Infections (Table 295-5)<br>Encapsulated organisms<br>Cytomegalovirus (pneumonia and gastroenteritis and ocular infections) | Cytomegalovirus remains a significant risk post-transplant in this period. Coexistence of chronic graft-versus-host disease worsens the prognosis of infections. |
| Infections with chronic graft-versus-host disease | — |
| Malignancy<br>Post-transplant lymphoproliferative disorder<br>Disease relapse | Decreasing immunosuppressant agents is the usual treatment for post-transplant lymphoproliferative disorder. |

## THE RENAL TRANSPLANT PATIENT:

- The preferred treatment for ESRF
- VASCULAR COMPLICATIONS:
  - Renal artery stenosis
  - Allograft infarction
  - Arteriovenous fistulas
  - Pseudoaneurysm
  - Renal vein thrombosis
- NONVASCULAR COMPLICATIONS:
  - Ureteral obstruction
  - Urine leak
  - Periallograft fluid collections (haematomas, lymphoceles and abscesses)
  - Neoplasms
  - Post-transplant lymphoproliferative disease
- MAJOR CAUSES OF DEATH/TRANSPLANT LOSS:
  - Chronic renal failure due to glomerulosclerosis and graft fibrosis
  - Vascular, malignant or infectious complications
- MEDICATION CHANGES OR USE OF CONTRAST (INCLUDING GADOLINIUM) NEED TO BE CLEARED BY THE TRANSPLANT TEAM

## DIAGNOSTIC TESTING:

- Serum creatinine is the most valuable prognostic function of graft function at all times after transplantation
- The urinalysis provides clues to acute changes in graft viability
  - Red cell casts and proteinuria are commonly seen in recurrent or de novo glomerulonephritis

    - Significant proteinuria may signal rejection, drug toxicity, glomerular diseaes or other graft nephropathy
- Cyclosporine or tacrolimus levels SHOULD BE TAKEN FOR ALL PATIENTS

**IMAGING IN THE RENAL TRANSPLANT PATIENT:**

- ULTRASONOGRAPHY:
    - The best test to detect urinary obstruction
    - Used in those suspected of having:
        - Pyelonephritis
        - Vascular abnormalities (stenosis, thrombosis, pseudoaneurysm, AV fistula)
        - Perinephric abscess
        - Urine leak
        - Wound infection
        - Rejection
- MRI:
    - Can be helpful in evaluating haematomas
    - Beware gadolinium contrast → can cause ARF in up to 3.5% and diffuse interstitial fibrosis in those with low GFR

**COMPLICATIONS IN THE RENAL TRANSPLANT PATIENT:**

- **INFECTIOUS COMPLICATIONS AND COMPLICATIONS FROM IMMUNOSUPPRESSANTS**
- Graft dysfunction and failure
    - Chronic renal dysfunction precedes the majority of graft failures
    - Acute renal failure in transplant patients is defined as a 20% rise from baseline serum creatinine (compared with 50% rise in normal patients)

| Table 295-10 Differential Diagnosis of Renal Allograft Dysfunction | |
|---|---|
| **Deferential Disorder** | **Comments** |
| Mechanical | At ultrasonography, a urine leak (i.e., urinoma) appears as a well-defined, anechoic fluid collection with no septations that increases in size rapidly. |
| Complications of surgery | |
| Ureteral obstruction | |
| Urine leak: urinoma, ascites, or abscess | |
| Vascular | The transplanted kidney is usually placed extraperitoneally in the right iliac fossa. End-to-side anastomosis to the external iliac vasculature provides circulation. Color duplex imaging of the renal artery and vein are helpful in assessing renal vascular stenosis or thrombosis.[57] |
| Renal artery stenosis or thrombosis (12%). | |
| Renal vein thrombosis. | |
| Renal artery and renal vein thrombosis are uncommon. They usually occur in the first month after transplant. | |
| Glomerulonephritis | |
| Infection | Urinary tract infections are the most common source of bacteremia in renal transplant recipients, and infectious diseases are the second leading cause of death in this population. See Infections in the Transplant Patient. |
| Urinary tract infection | |
| Interstitial nephritis from polyoma BK virus, cytomegalovirus, herpes viruses 1 and 2, and adenovirus | |
| Rejection | Most common presentation of rejection in renal transplant patients is hypertension and falling urine output. Comparison of creatinine at the time of presentation to prior levels is critical. Fever may be a presentation for rejection. |
| Hyperacute | |
| Acute | |
| Late (recurrent acute) | |
| Chronic cellular | |
| Chronic humoral | |
| Recurrent pyelonephritis/vesicoureteral reflux | — |
| Nephrotoxic agents | Drug serum levels do not correlate well with the degree of renal damage. NSAIDs are contraindicated in this group. Avoid contrast agents if possible. |
| Aminoglycosides, fluoroquinolones, cidofovir, foscarnet, sulfonamides, calcineurin inhibitors (cyclosporin A and tacrolimus), NSAIDs, gadolinium-based and some other contrast agents, herbal preparations | |
| Noncompliance with | Diabetes often follows transplantation; marked exacerbations in hypertension are frequently associated with graft failure. |
| Medications | |
| Management of risk factors such as diabetes and hypertension | |
| Chronic allograft nephropathy | — |

## THE LIVER TRANSPLANT PATIENT:

- Liver transplantation is widely accepted as an effective therapeutic modality for a variety of irreversible acute and chronic liver disease
- CLINICAL FEATURES:
    - Consult the transplant team early for suggestions on what work up should be done
    - Problems seen in ED related most commonly to:
        - Bleeding
        - Rejection
        - Infection
        - Biliary, vascular and wound complications
- Usual lab assessments as well as cultures of blood, urine, bile and ascites (if present)
- Abdominal US with Doppler flow studies ➔ can rule out fluid collections, thrombosis of the hepatic artery or portal veins
    - Identifies any dilation of the biliary tree ➔ patients may require ERCP for complete evaluation
- EARLY BROAD SPECTRUM ANTIBIOTICS ADVISED
- **See earlier sections for discussion on infectious complications and complications due to immunosuppressant drugs**

| Table 295-11 Specific Complications of Liver Transplant | |
|---|---|
| **Complication** | **Comments** |
| Bleeding complications | GI bleeding should be managed in the usual fashion but may signal graft dysfunction. |
| Biliary complications | Bile leaks present early and biliary strictures present late—>2 mo from transplant. In both cases, cholestatic liver enzymes are elevated, typically with right upper quadrant pain (more pronounced with bile leak). |
| Bile leak | |
| Biliary stricture | |
| Hepatic artery complications | CT with contrast (if renal function adequate) or US are helpful in the evaluation of these conditions. |
| Hepatic artery thrombosis | |
| Hepatic vein thrombosis | |
| Portal vein complications | |
| Rejection | Early alkaline phosphatase and bilirubin levels rise, followed by a rise in aspartate aminotransferase and alanine aminotransferase. |
| Neurologic complications | Causes include hemorrhage, cerebrovascular infarct, cerebral abscess, hypertensive encephalopathy, osmotic demyelination syndrome, and sinus thrombosis. MRI best for evaluation. |
| Malignancy | Increased risk for squamous cell carcinoma, lymphomas, and post-transplant lymphoproliferative disorder (see Post-Transplant Lymphoproliferative Disorder in the General Complications to Transplant Patients section). |

## THE LUNG TRANSPLANT PATIENT:

- Advances in donor and recipient selection, improved surgical techniques as well as new immunosuppressive drugs and better management of infections has improved survival

| Table 295-11.1 General Indications for Single-Lung, Double-Lung, and Heart-Lung Transplantation |
|---|
| Conditions requiring single-lung transplantation (primarily parenchymal conditions) |
| Emphysema or COPD (most common) |
| IPF |
| $\alpha_1$-Antitrypsin deficiency |
| Primary pulmonary hypertension |
| Eisenmenger syndrome |
| Others (sarcoidosis, eosinophilia, lymphangioleiomyomatosis, bronchiolitis obliterans, retransplantation) |
| Conditions requiring double-lung transplantation (primarily infectious conditions) |
| Cystic fibrosis (most common) |
| Selective patients with COPD (second most common) |
| IPF |
| $\alpha_1$-Antitrypsin deficiency |
| Primary pulmonary hypertension |
| Bronchiectasis |
| Eisenmenger syndrome |
| Conditions requiring heart-lung transplantation (primarily vascular conditions) |
| End-stage lung disease with nonrepairable congenital cardiac defects |
| Eisenmenger syndrome secondary to advanced valvular or ischemic cardiomyopathy |

- CLINICAL FEATURES:
    - Important features to note ➔ RR, pulse oximetery, cyanosis, diaphoresis, use of respiratory muscles, signs of congestive heart failure, adequacy of peripheral perfusion
    - CXR to identify infiltrates or pneumothorax
    - Pulmonary function tests (but this cannot distinguish between acute rejection, infection, nonimmunologic causes of respiratory dysfunction such as airway stenosis)
        - A drop in FEV1 of >10% is considered a significant change that warrants clinical investigation ➔ patients should measure their FEV1, BP and temperature daily
- DIFFERENTIATING INFECTION FROM REJECTION:
    - BRONCHOSCOPY IS NEEDED TO ADEQUATELY DISTINGUISH THESE TWO CLINICAL ENTITIES
        - The two OFTEN OVERLAP in terms of their symptoms and signs
        - Management is quite different
        - Urgent bronchoscopy with BAL and transbronchial biopsy is required to discern the specific aetiologies
    - COVER BOTH INFECTION AND REJECTION TO BEGIN WITH
- EARLY COMPLICATIONS OF LUNG TRANSPLANT:

**Table 295-12 Time Course of Lung Transplant Complications**

| Days Post-Transplant | Complications Most Commonly Seen in Each Time Period |
|---|---|
| 0–3 d | Hemorrhage from technical/mechanical problems |
| | Reperfusion injury |
| | Dysrhythmia |
| 3 d–1 mo | Infection: bacterial, mycoplasma, community respiratory viruses |
| | Rejection |
| | Anastomotic failure |
| | Pulmonary embolism |
| | Muscle weakness |
| | Dysrhythmia |
| Starting at 1 mo | Rejection |
| | Obliterative bronchiolitis |
| | Infection |
| | Bacterial, fungal, community respiratory viral (can occur at any later time) |
| | Mycoplasma 0–4 mo |
| | Mycobacteria after 4 mo |
| Other | Cytomegalovirus infection and *Pneumocystis jiroveci* pneumonia may occur any time, but are more common when prophylaxis is not being given, especially when such treatment has been recently discontinued. |

    - ACUTE REJECTION:
        - TREATMENT SHOULD BE DISCUSSED WITH THE PATIENT'S TRANSPLANT TEAM
        - If maintenance immunosuppressant regimen has been tapered, return to pretaper dosages

        - High-dose corticosteroids (15mg/kg IV methyprednisolone daily for three days) then 1mg/kg prednisone for 10days
        - Acute rejection is common and may occur 3-6 times in the first postoperative year
        - After the first year, the frequency of acute rejection decreases
        - SIGNS OF REJECTION ➔ cough, chest tightness, increase or decrease in temperature from baseline >0.28C, hypoxaemia, decline of FEV1>10%, development of infiltrates on CXR (may be radiographically silent after six weeks)
        - Clinical response to treatment is gauged by improvement in oxygenation, spirometry and radiographic appearance and typically occurs within 24-48 hours after treatment is initiated
    - INFECTION:
        - One of the most common causes of morbidity and mortality in lung transplant patients (see below for others)

**Table 295-14 Causes of Death in Adult Lung Transplant Recipients**

| Cause of Death | Percentage at <1 mo* | Percentage at 1–12 mo* | Percentage at 1–3 y* | Overall Percentage† |
|---|---|---|---|---|
| Graft failure | 28 | 19 | 18 | 5.3 |
| Infection, non-cytomegalovirus | 20 | 36 | 24 | 63.1 |
| Cardiovascular | 11 | 4 | 3 | — |
| Bronchiolitis obliterans | 0.4 | 5 | 28 | — |
| Malignancy | 0.2 | 5.4 | 7.8 | — |
| Acute rejection | 4.7 | 2 | 1.9 | — |
| Technical | 8 | 3 | 1 | |
| Pulmonary embolism | — | — | — | 5.3 |
| Acute myocardial infarction | — | — | — | 5.3 |
| Other | 27 | 22 | 15 | — |

        - Infection of donor lungs is frequently found on cultures taken before transplantation (staph aureus may be more prevalent in donor lungs given high rates among ventilated brain injury patients)
- INDICATIONS FOR HOSPITAL ADMISSION

| Table 295-13 Indications for Hospital Admission for Lung Transplant Patients |
|---|
| Pretransplant patients |
| Respiratory failure |
| Infiltrate |
| Systemic infection |
| Decompensated congestive heart failure or pulmonary edema |
| Pneumothorax |
| Post-transplant patients |
| Respiratory failure |
| Acute rejection |
| Rapidly progressive airflow limitation (forced expiratory volume in 1 second falls >10% over 48 h) |
| Infiltrate |
| Systemic infection |
| Febrile neutropenia |
| Pneumothorax |

## THE CARDIAC TRANSPLANT PATIENT:

### ADULT TRANSPLANT RECIPIENTS:

- Indicated for patients with end-stage heart failure not remediable by standard medical or surgical therapy
- BRIDGED ON CARDIAC ASSIST DEVICES (LVAD)
- Predominant diagnoses in kids are DILATED CARDIOMYOPATHIES AND CONGENITAL HEART DISEASE

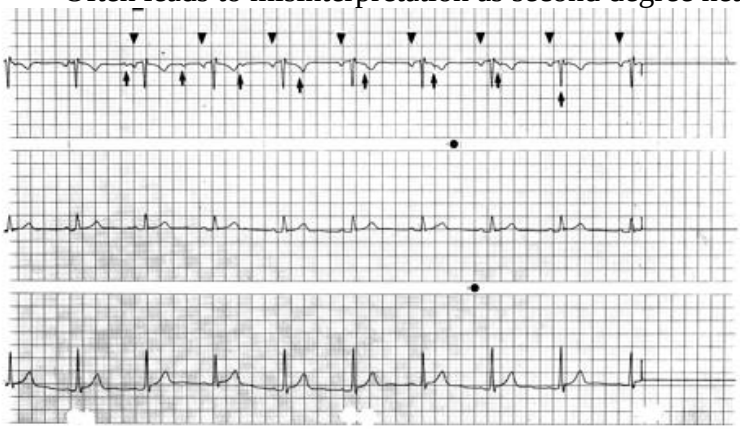
### CARDIAC PHYSIOLOGY AFTER TRANSPLANTATION:

- The success of a heart transplantation operation depends on the ability of the denervated heart to support the normal circulation
- The lack of sympathetic and parasympathetic innervation, does, however induced an ALTERED PHYSIOLOGIC STATE
    - Normal sinus rhythm with a rate between 90-100
    - Absence of the initial centrally mediated tachycardia in response to exercise
        - BUT THE HEART REMAINS RESPONSIVE TO CIRCULATING CATECHOLAMINES OR ENDOGENOUS AND EXOGENOUS ORIGIN
        - With exercise, cardiac output increases in response to increased PRELOAD and circulating catecholamines and patients should be able to return to vigorous exercise or premorbid activities

### PATIENT EVALUATION:

- With both techniques of allograft implantation, the donor heart is implanted with its OWN SINUS NODE INTACT to preserve normal AV conduction, but the current techniques also result in preservation of the recipient's sinus node at the superior cavoatrial junction

- The atrial suture line renders the two sinus nodes electrically isolated form each other
- Hence ECGs frequently will have two distinct P waves
  - Often leads to misinterpretation as second degree heart block





ECG in a heart transplant patient. ECG demonstrating donor and recipient P waves (*arrowhead* = donor P wave; *arrow* = recipient P wave).

**Table 295-15 Etiology of Heart Failure in Adult Transplant Recipients**

| Adult | Occurrence (%) |
|---|---|
| Coronary artery disease | 45 |
| Dilated cardiomyopathies | 45 |
| Valvular | 4 |
| Retransplantation | 2 |
| Congenital | 2 |
| Miscellaneous | 2 |

**Table 295-16 Etiology of Heart Failure in Pediatric Transplant Recipients**

| | Age | | |
|---|---|---|---|
| **Diagnosis** | **Percentage at <1 y** | **Percentage at 1–10 y** | **Percentage at 11–17 y** |
| Congenital artery disease | 75 | 37 | 24 |
| Dilated cardiomyopathies | 20 | 50 | 62 |
| Retransplantation | 1 | 5 | 4 |
| Other | 4 | 8 | 10 |

**IMAGING:**

- Echo is a useful tool for evaluation of cardiac function and interpretation is routine, other than for the presence of evaluation of atrial size ➔ biatrial dilatation is common and has no adverse implications for cardiac function
  - Early rejection results in diastolic dysfunction but this is difficult to detect
  - Severe rejection will be accompanied by signs of biventricular enlargement with global hypokinesia and significant AV valve regurgitation

- CXR may show “cardiomegaly” but this is often due to larger donor heart being transplanted

## COMPLICATIONS AFTER CARDIAC TRANSPLANT

**Table 295-17 Complications after Cardiac Transplant**

| Complication | Comments |
|---|---|
| Altered physiology | See Cardiac Physiology after Transplantation section |
| Dysrhythmias | Dysrhythmias after transplantation are frequently due to rejection. Treat the unstable patient presenting in extremis with 1 gram of methylprednisolone IV; delay rejection therapy in the stable patient for consult with the transplant team and biopsy. Atropine has no effect due to denervation. |
| Sinus node dysfunction | Theophylline may be of benefit, pacemaker usually required. |
| Pulmonary complications | Diagnosis may require CT or more invasive diagnostic procedures. |
| Pneumonia | |
| Thromboembolic disease | |
| Exercise-induced hypoxemia | |
| Pneumothorax | |
| Interstitial fibrosis | |
| Cardiac ischemia | Patients do not experience pain due to denervation; symptoms typically occur with complications such as congestive heart failure. |
| Rejection | Treat the patient presenting in extremis; withhold treatment for biopsy if possible. |
| Infection | See prior section Infections in the Transplant Patient |
| Congestive heart failure | Echocardiography can help to determine etiology and therefore ideal treatment. |
| Ischemic stroke and intracranial hemorrhage | Increased risk after heart transplant. |
| Complications specific to ventricular assist devices | Increased risk of infection and thromboembolism. |
| Cardiac allographic vasculopathy | Pediatric heart transplant recipients are at risk for graft coronary artery disease and ischemia. May require retransplantation. |

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## CORNEAL TRANSPLANTATION:

- The most common form of human solid tissue transplantation and usually does not require systemic or permanent immunosuppression but allograft rejection remains the leading cause of graft failure in corneal transplantation

## COMPLICATIONS OF CORNEAL TRANSPLANTATION:

- REJECTION:
    - Irreversible immune rejection is the major cause of allograft failure in both the intermediate and late post-op phases

    - Inflammatory process starts at the margin nearest the proximal vessels and may manifest with cloudiness of the cornea or anterior chamber inflammatory cells
    - Patients may be asymptomatic but may have mild-severe pain, photophobia, decreased visual acuity
    - Late graft failure may present with keratitic precipitates
    - Can present with endophthalmitis with hypopyon and vitreous infiltrates
    - CHILDREN ARE MORE LIKELY TO DEVELOP REJECTION
    - TREATMENT ➔ topical steroids are the mainstay of graft rejection, plus topical/systemic cyclosporine
- WOUND DEHISCENCE:
    - Can occur early or many years later
    - There may be globe rupture, slight separation or just broken sutures
    - Infection and trauma are the two most common causes
- INFECTION AFTER CORNEAL TRANSPLANT:
    - HERPETIC KERATITIS:
        - Recurrence in those who have had this previously
- BACTERIAL KERATITIS:
    - Associated with a high incidence of graft failure and poor visual outcome
    - Consult transplant team for choices of antibiotics ➔ vancomycin, cephazolin (gram positive cover), ceftazidime (gram negative cover)
- SUTURE-RELATED INFECTION:
    - Loose or broken sutures are a risk factor for infection ➔ can lead to abscess, erosions, conjunctival inflammation, tarsal conjunctival ulceration, lid oedema and graft rejection