

Special Commentary
Overcoming the Hurdle of Post Transplant Infection

Rajapurkar M M, Gohel K
Department of Nephrology, Muljibhai Patel Urological Hospital and Society for Research in Nephro-urology, Dr. Virendra Desai Road, Nadiad, Gujarat – 387001. E-mail: mmr@icenet.net, gohelk2000@yahoo.co.in

Among the solid organ transplantation, kidney transplantation is associated with the lowest rates of infection, in part because of the elective or semi elective nature of kidney transplantation. Despite ongoing refinements in immunosuppressive agents, graft preservation and surgical techniques, infection remains a significant cause of morbidity and mortality in renal transplant recipients. Infections related to transplant surgery or post operative infections nosocomial, opportunistic or latent pathogens could affect graft function and transplant outcome. Graft dysfunction or chronic rejection leads to augmented immunosupression increasing the risk of infection with immunomodulating viruses.

Infections syndromes encountered in kidney transplant recipient include device associated infection, genitourinary infection, including infection associated with anti microbial resistant organisms, bacterial, mycobacterial and fungal pneumonia, including pulmonary and disseminated infections with nocardia, mycobacteria spp. and candida, aspergillus, cryptococcus and pneumocystis fungi, reactivation mycoses such as histoplasmosis and coccidioidomycosis and disseminated or organ specific viral diseases like CMV(cytomegalovirus), HHV – Human herpes virus, varicella zoster virus(VZV), Epstein barr virus(EBV), polyoma virus, adenovirus and respiratory viruses including influenza A and B, respiratory syncitial virus(RSV) and para influenza virus.

RISK FACTORS
Various risk factors have been related to patient’s pre-transplant status preoperative & postoperative condition as well as duration and immunosuppression

Pretransplant Risk Factors
- Medical conditions (renal failure, diabetes, malnutrition).
- Immunosuppression for chronic conditions like corticosteroids, cyclophosphamide.
- Unrecognized or inadequately treated infection.
- Preoperative antibiotic exposure.
- Colonization with unusual or resistant organism
- Duration and frequency of hospitalizations

Preoperative Risk Factors
- Complexity of surgery and requirement for reexploration.
- Prolonged operative time
- Graft injury of prolonged ischaemia: acute graft failure.
- Bleeding or multiple blood transplantation
- Preoperative bacteraemia or sepsis
- Contamination of preservation fluid or graft
- Retained foreign bodies

Post transplantation Risk Factors
- Acute graft failure or dysfunction: requirements for augmented immunosuppression and prolonged cytolytic therapy.
- Prolonged cauterizations, genitourinary stents or mechanical ventilation.
- Anastomotic breakdown or leaks, fluid collection, devitalized tissues, haematoma.
- Leucopenia, thrombocytopenia, acquired hypogammaglobulinaemia
- Prolonged antibiotic therapy, acquisition of anti-biotic resistant nosocomial pathogens.
- Development or worsening of medical condition like hyperglycaemia, hepatic disease, respiratory failure, altered sensorium
- Hospital exposures: construction, ventilation and water supply.
- Leak of appropriate hand hygiene by caregivers.
Timetable for occurrence of post transplant infection

During months 1 to 6 infections associated with postoperative complications or with enhanced immunosuppression can develop persist or recur. Augmented immunosuppression is associated with an increased risk of infection with immunomodulating viruses that enhance susceptibility to opportunistic infection by altering the expression of inflammatory mediators and cytokines.

After post transplant month 6, patients can be categorized as those with good graft function and minimal long-term immunosuppression, those with poor graft function due to chronic rejection who require intensified immunosuppression, or those chronically infected with immunomodulating viruses such as CMV, HCV.

BACTERIAL INFECTION

Approximately 80% of infections in the kidney transplant recipient are bacterial. Most bacterial infections occurring in the first month after transplantation are similar to those occurring after genitourinary surgery in immunocompetent patients and the risk of infection increase with the complexity of transplant surgery.

Pulmonary Infections

These are the most common life threatening infections in the kidney transplant recipients. The risk of pneumonia is increased among patients who required prolonged intubations, structural lung disease, and those with diminished gag reflex, prolonged usage of nasogastric tube, or impaired diaphragmatic function that increase the risk of aspiration. Hospital acquired species like legionella or pseudomonas from contaminated water or aerosols also increases the risk of pneumonia.

Most common bacteria encountered are P. aeruginosa, S. pneumonia, enterobacteriaceae, S. aureus, nocardia, legionella, mycobacteria including M. Tb., mixed flora.

Urinary tract Infections (UTIs)

Urinary tract is the second most common site of infection with bacteria. The risk of UTIs is directly related to surgical complications like urine leaks, wound haematomas, lymphocele that can result in bacterial suprainfection. Genitourinary tract manipulation during transplantation, urinary catheters, anatomic abnormalities and neurogenic bladder also predispose to UTIs. Fever, graft tenderness and a characteristic ultrasound appearance assist in diagnosis. Common organisms include enteric gram negative bacilli, staphylococci, enterococci and rarely, anaerobic bacteria.

Wound Infection

The incidence of surgical wound infection ranges from 2% to 25%. It typically occurs within 3 weeks and usually related to technical complications and recipient factors, such as diabetes and obesity.
sity. It can involve the perinephric space or cause mycotic aneurysm of anastomotic site. Rarely allograft nephrectomy is required.

Other infections

Less common infections in kidney transplant recipients include sinusitis associated with nasogastric tube or nasotracheal tube, cannulation site infection, prostatitis and prostatic abscess associated with urinary catheters.

Diagnostic Methods

Pulmonary Infection

Diagnostic specimens for this infection are blood, expectorated sputum, tracheal suction, bronchoalveolar lavage (BAL) fluid, transthoracic fine needle aspiration, and occasionally lung biopsy. Blood culture may assist in the diagnosis because 10 - 15% of patients with pneumonia may have bacteria. Fibreoptic bronchoscopy with BAL and transbronchial biopsy is valuable in patients with accessible lesion. Nocardia species can be identified with modified AFB stain which reveals as delicately branching filamentous, beaded grampositive rods. Apart from AFB staining, BACTEC culture technique, identification of specific DNA probes can decrease the time of diagnosis of mycobacterial infection. Certain species like legionella may require charcoal media or specific nucleic acid probes or directs fluorescent antibody testing for specimens. HRCT (High Resolution Computed Tomography) is valuable in the differential diagnosis of pneumonia and can be used to guide lung biopsy.

UTI

Clean catch midstream urine specimen should be enough for routine culture. Infected perigraft collection or devitalized tissues will often require percutaneous or open incision, in addition to antimicrobial therapy to resolve the infection.

Wound and other Tissue infections

Diagnosis should include aspiration of any drainable material, deep swab specimen form the site, and a biopsy specimen when appropriate. US or CT guidance may be needed in localization and drainage of deep collection. Patients with diarrhoea, colitis or abdominal symptoms should have stool specimen.

Bacteria / Fungaemia

Blood cultures should be drawn ideally before initiation of antimicrobial therapy. Specimens should be collected using both blood cultures and fungal isolation tubes. Fungal cultures are especially important if the patient has received steroids pulses, has diabetes mellitus, indwelling catheters, or receiving total parenteral nutrition. Renal transplant recipients may not have systemic signs such as fever or leucocytosis with sepsis; consequently, a lower clinical threshold for bacteraemia and sepsis is warranted in these patients.

PRINCIPLES OF ANTIMICROBIAL THERAPY

Surgical Prophylaxis

Perioperative antimicrobial prophylaxis reduces the frequency of surgical site infections. The agent should have activity against skin pathogens (e.g. staphylococcal, streptococcal) and urinary tract pathogens (e.g. E. coli, Klebsiella, Proteozoa). Cefazolin (1 to 2 gram) is generally preferred and should be administered within 1 hour of the surgical incision. This should be given as a single dose or discontinued after no more than 24 hours to minimize the risk of toxicity and super infection, and limit cost.

Empiric Therapy

For patients with suspected sepsis, the choice of antimicrobial therapy should be guided by the potential site(s) of infection and bacterial or fungal pathogen, time since transplantation, the severity of hepatic and renal dysfunction, net state of immunosuppression, institution specific susceptibility pattern, prior antibiotic therapy. Commonly used agents for empiric therapy are broad-spectrum penicillins (piperacillin), 3rd generation cephalosporins (Ceftriaxone, Ceftizoxime, Cefotaxime), B-lactam plus B-lactamase inhibitor combination (ampicillin/subactum, piperacillin/tazobactum, ticarcillin/Clavulanate), Carbapenem (Imipenem, meropenem) or Vancomycin; if line associated infection is suspected.

Specific Therapy

With the isolation of specific organism, therapy is focused on the specific pathogen to minimize the risk for super infection, toxicity and cost of therapy.

FUNGAL INFECTIONS

Although the incidence of fungal infections in renal transplant is less than that reported for other organ transplantation, the mortality remains high and is related to the pathogenicity of organisms, site of infection, impaired host inflammatory response, limited diagnostic tools, potential for rapid clinical progression, failure to recognize high risk patients and comorbidities like renal failure and diabetes mellitus.

Fungal colonisation occurs frequently with renal transplant patients because immunosuppression in-
<table>
<thead>
<tr>
<th>Pathogens</th>
<th>Suggested Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus, methicillin susceptible</td>
<td>Oxacillin, nafcillin, First generation cephalosporin, Vancomycin (if penicillin allergic)</td>
</tr>
<tr>
<td>S. aureus, methicillin resistant</td>
<td>Vancomycin, quinupristin/dalfopristin, linezolid, daptomycin</td>
</tr>
<tr>
<td>Enteric gram-negative bacilli</td>
<td>Third-generation cephalosporin, antipseudomonal penicillin + aminoglycoside, quinolones (ciprofloxacin, levofloxacin) carbapenem, TMP - SMX</td>
</tr>
<tr>
<td>Streptococcus pneumonia, penicillin susceptible</td>
<td>Penicillin G, ampicillin, second or third generation cephalosporin</td>
</tr>
<tr>
<td>S. pneumoniae, highlevel penicillin resistant</td>
<td>Levofloxacin, gatifloxacin, moxifloxacin, vancomycin</td>
</tr>
<tr>
<td>Legionella pneumophila</td>
<td>Erythromycin (+ rifampin), clarithromycin, azithromycin, quinolone</td>
</tr>
<tr>
<td>Mycobacteria tuberculosis</td>
<td>Isoniazid, rifampin, pyrazinamide and ethambutol, alternative agent intolerance (e.g. quinolone, streptomycin)</td>
</tr>
<tr>
<td>Atypical mycobacteria</td>
<td>Determined by sensitivities of individual species (extended susceptibility testing recommended)</td>
</tr>
<tr>
<td>Nocardia asteroids</td>
<td>TMP - SMX, sulphisoxazole, minocycline, amikacin, imipenem, ceftriaxone, cefuroxime</td>
</tr>
</tbody>
</table>

Including corticosteroids, usage of broad-spectrum antibiotics, presence of urinary catheters, vascular catheter and endotracheal tubes and domiciliary exposure. Colonisation defined as the isolation of yeast or mold from a non-sterile body site without local or systemic evidence of infection. In the post transplant period, differentiating between fungal colonisation and infection is often difficult and remains imprecise.

Candida spp., Aspergillus spp., and C. neoformans spp., are the most common post transplant fungal infection. P. carinii, Zygomyces, Hyalohyphomycoses, Phaeohyphomycosis, and the geographically restricted mycoses (histoplasma, Blastomycetes, Coccidioides) are commonly encountered under special clinical circumstances, such as immunomodulating virus infection, reactivation, or residual disease for endemic mycoses, chronic graft dysfunction or during the treatment of post transplant malignancy.

**Candida** infection occurs most commonly during the first month and commonly associated with technical complexities and complication of the renal transplant surgery or with early rejection and enhanced immunosuppression. Spectrum of Candida infections includes mucocutaneous candidiasis and oesophagitis, wound infection, intraabdominal infection, cystitis, pyelonephritis and ureteral obstruction, intraabdominal infection, peritonitis and indwelling device-associated fungaemia.

**Pneumocystis** occur most commonly during period between 1 and 6 months especially when patients are receiving increased dose of corticosteroid or inadequate prophylaxis. Typically occurs with fever, nonproductive cough, shortness of breath, hypoxia, with interstitial infiltrates and consolidation on chest radiograph. BAL with TBB is highly sensitive to demonstrate pneumocystis carinii. First line agent is TMP-SMX(14 to 21 days) while second line agents are IV pentamidine, Dapsone-trimethoprim, atovaquone.

Rest all other fungal infections occur 6 months or more after kidney transplantation.

**Cryptococcus** infection presents with cryptococcal meningitis, SOL in brain, pulmonary, dermatological, skeletal, organ specific disease. This fungal infection can be diagnosed by antigen detection in serum, urine, CSF by latex agglutination, coagglutination, EIA, antibody detection in serum, CSF by IgG, IgM, nucleic acid detection by PCR from serum, BAL, CSF and cultures, India ink stain.

**Zygomyces** with Rhizopus and mucor species presents with pulmonary, rhinocerebral and cuta-
neous disease. Zygomycosis can be diagnosed with smear revealing sparsely septate broad hyphae and culture. Radiology in form of CT/MRI may reveal consolidation, pleural effusion and focal cavitation. It also helps in determining the extent of infection, prognosis and monitoring response to therapy.

**Aspergillus** infection presents with pneumonia and other tissue invasive infection including, genitourinary, CNS, rhino-cerebral, gastrointestinal, skin, wound and musculoskeletal disease. Aspergillus infection can be detected by antigen detection by detection of galactomannan in serum, BAL, urine or CSF by EIA, Latex agglutination, nucleic acid detection by PCR, culturing respiratory or sterile specimens, antibody detection or direct visualization by histopathology examination. Radiological examination in form of plain X-ray, CT or MRI may help in determining the diagnosis and extent of disease.

**Coccidioidomycosis** manifests as pneumonia, meningitis and skin involvement. This infection can be detected by serology, histopathology, and culture. Radiology may supplement the diagnosis.

**Histoplasmosis** is manifested by pneumonia, mediastinal, and cutaneous disease or disseminated disease and detected by same techniques.

**Principle of anti fungal therapy**

Invasive candidiasis, cryptococcosis, coccidioidomycosis, aspergillosis, histoplasmosis, all treated with amphotericin B. High doses 1-1.5 mg/kg/d may require for invasive CNS involvement. Lipid formulations like liposomal, lipid complex, colloidal dispersion are associated with lesser nephrotoxicity and metabolic derangements. Voriconazole is equal or superior to conventional amphotericin for the treatment of invasive aspergillosis. Fluconazole, itraconazole can be used for mild to moderate fungal infection. Echinocandins including caspofungins can be used for fluconazole resistant species.

**VIRAL INFECTION**

Viral infection is a major problem in renal allograft recipient, most commonly 1 to 6 months after transplantation. Clinical disease can occur later also after intensification of immunosuppression or physiologic insult that increase the net state of immunosuppression.

**CMV** cytomegalovirus infection occurs primarily after the first month with an estimated incidence of 30% to 78% if prophylaxis is not administered. In general dose type duration and intensity of immunosuppression determine the risk of CMV disease.

<table>
<thead>
<tr>
<th>Pathogens</th>
<th>Suggested Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryptococcus neoformans</td>
<td>Fluconazole, itraconazole, AmB + flucytosine, LFAB</td>
</tr>
<tr>
<td>Aspergillus species</td>
<td>AmBd, LFAB, voriconazole</td>
</tr>
<tr>
<td>Coccidioides immitis</td>
<td>AmBd, fluconazole, itraconazole, LFAB</td>
</tr>
<tr>
<td>Histoplasma capsulatum</td>
<td>AmBd, itraconazole, LFAB</td>
</tr>
<tr>
<td>Candida albicans</td>
<td>AmBd, fluconazole, voriconazole, itraconazole, LFAB, caspofungin</td>
</tr>
<tr>
<td>Non-albicans Candida sp.</td>
<td>AmBd, LFAB, caspofungin, itraconazole, (susceptible Candida sp. only and higher doses may be necessary)</td>
</tr>
<tr>
<td>Pneumocystis carinii</td>
<td>TMP - SMX, pentamidine, dapsone + TMP, atovaquone</td>
</tr>
</tbody>
</table>

Specific risk factors are donor recipient CMV mismatching, use of lymphocyte depleting preparation like induction and anti rejection therapy, comorbid illnesses, neutropenia and coinfection with HHV 6 and 7.

Active CMV infection may be symptomatic or asymptomatic and is characterized by viral replication and shedding with specific immune response to CMV. Primary infection represents infection in previously uninfected seronegative host. Secondary infection represents infection in a previously infected host caused by reactivation, reinfection or superinfection. Acute CMV infection can be divided further into CMV syndrome (Fever, fatigue, leucopenia, thrombocytopenia, increased CMV titer from a specific diagnosis assay) and invasive CMV disease (pneumonitis, hepatitis, gastrointestinal involvement like colitis, enteritis, involvement of renal allograft). Latent CMV infection represents lifelong persistence of virus without replication in healthy seropositive host. Recurrent CMV disease is defined as clinical manifestation of CMV disease arising after cessation of CMV treatment.

Refractory CMV disease may reflect viral resistance resulting from mutation in CMV strains or dis-
ease in a profoundly immunosuppressed host. CMV infection is associated with immunomodulation and dysregulation and may predispose to opportunistic infection, allograft rejection and in the development of PTLD - post transplant lympho proliferative disorder.

CMV disease can be diagnosed by viral culture – conventional culture, shell vial, nucleic acid detection by PCR, PP65 antigenemia, CMV IgG, IgM and by histopathology including light microscopy, immunohistochemistry and electron microscopy.

Treatment for CMV infection is IV Ganciclovir for 14 to 21 days. Oral valganciclovir may be effective for mild to moderate disease. After treatment low risk patients should be monitored and high-risk patients should receive maintenance therapy with oral ganciclovir or valganciclovir. Other agents cidovir and foscartern can be used to treat ganciclovir resistant strains. Addition of CMV hyperimmunoglobulin or IVIG may be helpful in clinical response.

BK virus - this polyomavirus causes latent infection of the kidney; with reactivation during immunosuppression, it may cause tubulointerstitial nephritis and ureteral stenosis and stricture. Primary infection presents between 10 days and 6 weeks and reinfection or reactivation presents between 5 weeks and 17 months. Definitive diagnosis requires renal biopsy. BK virus DNA PCR of urine and serum and the identification of decy cells in urine may assist. Management involves reduction of immunosuppression with close monitoring for rejections. Ieflunamide, cidovir, IVIG may be of clinical benefit.

HSV herpes simplex virus infection typically occurs within the first 6 weeks after transplantation and most commonly involves mucosal surfaces. Occasionally disseminate to visceral organs and causes hepatitis, pneumonitis, oesophagitis. Acyclovir is initially the treatment of choice. For severe infection intravenous acyclovir should be used. Alternative agents are valacyclovir, ganciclovir, and fenciclovir.

VZV varicella Zoster Virus infection develops in approximately 10% of renal transplant due to reactivation and presents with bullous eruptions & pain involving 2 to 3 adjacent dermatomes. The same agents used for HSV infection should be used for this infection.

Parvovirus - B 19 infection causes refractory severe anaemia, pancytopenia, thrombotic microangiopathy, fibrosing cholestatic hepatitis and graft dysfunction. 80% of infection occurs within 3 months of transplant. Bone marrow examination reveals typically giant proerythroblasts. B 19 virus DNA in serum can confirm diagnosis by PCR assays. Management consists of high dose IVIG and reduction of immunosuppression.

Human papillomavirus causes cutaneous and anogenital warts and is associated with cervical intraepithelial neoplasia, squamous cell carcinoma and anogenital carcinoma. Treatment includes topical keratolytic and caustic agents, topical and oral retinoids, podophyllin, 5-fluorouracil, bleomycin, physical ablation, and investigational immunotherapy.

Other human herpes viruses like HHV -6 is associated with hepatitis, pneumonitis, encephalitis. Symptomatic HHV -6 infection should be treated with antiviral agents and reduction of immunosuppression. HHV -7 manifestations are unclear. HHV-8 is associated with kaposi's sarcoma and diagnosis is supported by pathology and by the presence of HHV-8 DNA sequences in the involved tissue.

Adenovirus can cause haemorrhagic cystitis, fever, renal dysfunction and rarely dissemination with pneumonia, hepatitis and death. Renal biopsy reveals ground glass like intranuclear viral inclusion bodies in tubular cells. Ribavirin with or without IVIG with reduction in immunosuppression has been used with some success.

EBV- Epstein barr virus primarily targets B-lymphocytes. It is associated with an array of disorders ranging from infectious mononucleosis to nasopharyngeal carcinoma and B cell lymphomas in immunocompromised hosts. EBV associated (PTLD) post transplant lymphoproliferative disease progress through stage I - infectious mononucleosis syndrome, stage II - cells with cytogenetic abnormalities and atypia and stage III - malignant monoclonal B cell lymphoma. Histopathology and virologic studies determine the diagnosis. Treatment consists of reduction in immunosuppression, anti viral agents like acyclovir, chemotherapy, radiotherapy. Recently rituximab - anti CD20 antibody has been used with success rate of almost 65%.

PREVENTION

As stated in P and SM prevention is better than cure. Prevention part is divided into

1. Pre Tx recipient and donor screening.
2. Post transplant prophylaxis
3. Immunization

Pretransplant recipient and donor screening

Untreated or unrecognized infection in the recipient can become clinically apparent in the post
transplant period. These can include intravascular device infection, pneumonia, cellulitis, periodontal abscess, or smoldering intraabdominal, hepatobiliary or genitourinary tract infection. For the living donor careful history of prior infections and exposures and of any current signs or symptoms of infections should be obtained and active infections should be treated when appropriate. It may be difficult to differentiate between an infection acquired from the allograft, from an exogenous source or from reactivation of latent disease in recipient. Serious complications of allograft-transmitted infection include disruption of vascular anastomosis, mycotic aneurysm, infective endocarditis and sepsis.

**Pretransplant screening should include**

- Underlying medical conditions
- Antibiotic and medication allergies and adverse reactions
- Chest radiograph (e.g. any evidence of active infiltrates, prior granulomatous lesions; scarring)
- Dental assessment
- History of sexually transmitted disease, high risk behaviours, infection, drug usage.
- PPD skin test with energy panel history of tuberculosis risk factors and exposure(s)
- Urine culture
- Endovascular repair or placement (e.g valve, vascular graft)
- CMV antibody
- Hepatitis B virus (HBV) surface antigen (HbsAg)
- Hepatitis C virus (HCV) antibody
- HIV 1 and 2 antibody
- Rapid plasma reaginin (RPR)

**Post transplant prophylaxis**

Antimicrobial prophylaxis with co-trimoxazole has reduced the infection with P. carinii, N. asteroides, L.monocytogenes, toxoplasmosis, S. pneumoniae, bacterial gastroenteritis, and also UTI. In practice two strategies are used to reduce CMV disease - universal prophylaxis and preemptive therapy. Former is to give anti CMV treatment to all at risk renal transplant recipients for a defined duration and later involves treatment of patients with laboratory evidence of CMV replication like PP65 antigenemia or detection of CMV DNA. Potential strategies for CMV prophylaxis is as

**Potential strategies for cytomegalovirus (CMV) prophylaxis**

<table>
<thead>
<tr>
<th>Prophylactic</th>
<th>CMV Serologies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regimens</td>
<td>D+, R- R+</td>
</tr>
<tr>
<td>Oral acyclovir</td>
<td>0</td>
</tr>
<tr>
<td>Ganciclovir or</td>
<td>+</td>
</tr>
<tr>
<td>valganciclovir</td>
<td>0</td>
</tr>
<tr>
<td>IV ganciclovir followed by oral ganciclovir Or valganciclovir</td>
<td>+</td>
</tr>
<tr>
<td>IV or oral ganciclovir and CMVIG</td>
<td>+</td>
</tr>
<tr>
<td>Oral valacyclovir</td>
<td>+</td>
</tr>
</tbody>
</table>

D+ = donor positive, R+ = recipient positive, D- = donor negative, R- = recipient negative.

**Immunization**

Initial visit for transplant evaluation is the time to review prior immunization status. Live attenuated vaccine such as MMR, BCG, OPV, intranasal influenza and varicella, should be administered no later than 4 to 6 weeks before transplantation to minimize vaccine derived infection in the posttransplant period. Live vaccines should be avoided in immunocompromised hosts who require immunosuppression before transplantation and in all patients after transplantation.

Inactivated vaccines that are safe to administer to transplant recipients, when appropriate include hepatitis A, B, intramuscular influenza A, B, pneumococcal, H. influenza B, N. meningitides, inactivated polio vaccine, and DPT. An accelerated schedule for hepatitis B immunization has been used before and after transplantation. The immunogenicity of the HBV vaccination must be assessed following the vaccination.

In 1982, hepatitis B vaccination was recommended for all susceptible haemodialysis patients and staff members. By 2001, 60% of patients and 89% of staff members had been vaccinated, with the incidence of HBV infection decreasing to 0.05% and the prevalence of HBsAg positivist in dialysis patients decreasing to 0.9%. Screening of blood products and later the decrease in numbers of blood transfusions with the advent of recombinant erythropoietin also contributed to the marked decrease in incidence of hepatitis B.

Recommended doses for adult on dialysis are either 40 µg of Recombivax HB administered at 0.1, and 6 months or 40 µg of Engerix-B administered at
<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Administration and schedule</th>
<th>Booster Doses</th>
<th>Contraindication and Precautions</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B recombinant vaccine</td>
<td>Engerix, 40 mg IM at 1,2,6 mo Recombivax, 40 mg IM at 0,1,6 mo</td>
<td>When anti-HBS titer &lt; 10 mU/L</td>
<td>Hypersensitivity to yeast, latex, or any component of the vaccine; multiple sclerosis</td>
<td>There must be 4 wk between doses 2 and 3 (Recombivax); brands may be used interchangeably</td>
</tr>
<tr>
<td>Influenza trivalent inactivated vaccine</td>
<td>0.5 mL IM annually, preferably in October or November</td>
<td>Not recommended</td>
<td>Hypersensitivity to eggs; latex allergy; acute febrile illness</td>
<td>Can be administered at the same time as pneumococcal vaccine; live influenza vaccine is not recommended</td>
</tr>
<tr>
<td>Streptococcus pneumoniae 23-valent polysaccharide vaccine</td>
<td>0.5mL SC or IM</td>
<td>Revaccination 5 y after first dose</td>
<td>Hypersensitivity to any component of the vaccine; acute febrile illness; severely compromised cardiovascular or pulmonary function</td>
<td>May be administered at the same time as influenza vaccine; currently, revaccination after a second dose is not routinely recommended</td>
</tr>
<tr>
<td>Tetanus toxoid</td>
<td>Primary immunization: 3 doses of 0.5 mL of either tetanus toxoid or tetanus/diphtheria toxoid IM with 4-8 wk between doses 1 and 2 and 6-12 mo between doses 2 and 3</td>
<td>0.5 mL every 10 y</td>
<td>Hypersensitivity to thiomersal; neurological reactions to tetanus toxoid; acute febrile illness; latex allergy</td>
<td>In areas where diphtheria poses a risk, tetanus/dephteria toxoid may be preferred to tetanus toxoid</td>
</tr>
<tr>
<td>Varicella live attenuated vaccine</td>
<td>0.5 mL (minimum, 1,350 PFU) SC; second dose of 0.5 mL 4-8 weeks later</td>
<td>Not recommended</td>
<td>Severe immunodeficiency, including immunosuppressive therapy, human immunodeficiency virus, leukaemia lymphoma, or other blood dyscrasias. Anaphylaxis to neomycin or hypersensitivity to any vaccine component including gelatin</td>
<td>Not routinely recommended; consider for patients awaiting renal transplantation; recipients of vaccine may be capable of transmitting the vaccine virus to close contacts for up to 6 weeks</td>
</tr>
<tr>
<td>Hepatitis A inactivated vaccine</td>
<td>1 mL of Havrix or Vaqta IM into the deltoid</td>
<td>6-12 mo later</td>
<td>Hypersensitivity to any component of the vaccine, including neomycin; latex allergy; febrile illness</td>
<td>Not routinely recommended; administer to patients with chronic liver disease, travelling to endemic areas, with intravenous drug use and male patients who have sex with men</td>
</tr>
</tbody>
</table>
Table 2
Vaccinations for Adult Renal Transplant Recipients

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Administration &amp; Schedule</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B</td>
<td>Administer before transplantation</td>
<td>not routinely recommended post transplantation</td>
</tr>
<tr>
<td>Influenza</td>
<td>0.5 mL IM annually, preferably in October or November</td>
<td>Household contacts also should be immunized</td>
</tr>
<tr>
<td>S Pneumoniae</td>
<td>0.5 mL SC or IM</td>
<td>Revaccination recommended 5 y after first</td>
</tr>
<tr>
<td>Tetanus toxoid</td>
<td>See Table 1</td>
<td>Administer booster every 10 y &amp; after penetrating Wound if last administration &gt; 5 y</td>
</tr>
<tr>
<td>Varicella vaccine</td>
<td>not recommended after transplantation</td>
<td>Consider immunizing seronegative household contacts: No \ isolation of household contacts post vaccination is necessary unless a rash develops</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>1 mL of Havrix or Vaqta IM into the deltoid</td>
<td>not routinely recommended; for selected populations;</td>
</tr>
</tbody>
</table>

0, 1, 2 and 6 months. Despite a greater dose of vaccine, haemodialysis patient are less likely to achieve protective antibody titers, defined as 10mIU/mL or greater. The median response rate to vaccination in haemodialysis patients is 64% (range, 34% to 88%) with the 3-dose schedule compared with 90% to 95% in adults with normal immune status. To assess the response to HBV vaccination in dialysis patients, HBV surface antibody (anti-HBs) testing should be performed 1 to 2 months after the primary series is completed. In patients who do not respond to the primary 3-dose series of vaccine, an additional 3-dose series is recommended with a 40% to 50% response to revaccination. A case-control trial showed that the risk for HBV infection was 70% less in vaccinated compared with unvaccinated long term haemodialysis patients.

The current CDC recommendation is to test levels of anti-HBs annually in dialysis patients. If anti-HBs titers decrease to less than 10 mIU/mL, a booster dose is recommended. A recent decision analysis showed that the current practice of screening for HBV immunity before immunization is more cost effective than administration of a yearly booster without screening.

To improve immunogenicity of the HBV vaccine in dialysis patients, alternative routes of vaccine administration have been attempted. The intradermal route may offer a greater seroconversion rate, but is technically more difficult to administer. It is not recommended by the current CDC guidelines, but may be the preferred route in patients who do not respond to the primary vaccination series. Other methods to improve the immune response to HBV vaccination include administration of adjuvants such as interleukin 2 and granulocyte-macrophage colony stimulating factor, have produced variable results and are not recommended. Administration of cytosine-guanine oligodeoxynucleotide has shown promise in animals and stage I to II trials of healthy volunteers. However, no data are available for patients with renal disease.

There is evidence that vaccination of patients before the initiation of dialysis may result in greater success rates. A recent prospective study examined the response to HBV vaccination based on the stage of CKD in a cohort of predialysis patients. Patients with higher levels of kidney function, based on Cockcroft-Gault and Modification of Diet in Renal Disease equations, were more likely to respond to HBV vaccination, and the level of kidney function was an independent predictor of seroconversion. Long-term immunogenicity and cost implications of this strategy need to be investigated further. A simulated model showed that for the predialysis immunization strategy to become cost effective, the price of the vaccine needed to decrease substantially.

Patients who are potential transplant candidates may derive the greatest benefit from HBV vaccination because of the increased morbidity and mortality associated with HBV infection after renal
transplantation. Mathurin et al showed that 10 years graft and patient survival was lower in HBsAg-positive than HBsAg negative renal transplant recipients. Response to HBV vaccination after renal transplantation appears to be poor. Lefebvre et al, using 40μg of HBV vaccine, reported a conversion rate of only 36%. Conversely, patients vaccinated before transplantation who were administered a booster of 40μg of the vaccine post transplantation had a conversion rate of 86%. Therefore, HBV immunization should be administered before transplantation.

Information on the use of pneumococcal vaccination in renal transplant recipients also is very limited. Kumar et al performed a randomised double-blinded trial comparing responses to pneumococcal conjugate and polysaccharide vaccines in 60 renal transplant recipients. Functional antibody responses were not different between the 2 groups. In both groups, overall response rate to each individual serotype of the vaccine were poor (13% to 50%). This response was much lower than in earlier studies, but at that time, different immunosuppressive protocols were used.

There were earlier concerns about influenza immunization triggering acute rejection episodes in recipients of renal transplants. This has not been substantiated in the literature. However, influenza infection itself was associated with acute rejection in 62% of 30 patients with influenza documented in solid organ transplant recipients at the University of Pittsburgh between 1990 and 2000. The response to influenza vaccination in recipients of renal transplants appears to be diminished. Sanchez-Fructuoso et al immunized 49 patients with a 1-year functioning transplant and compared them with 37 healthy family members. The proportion of renal transplant patients able to produce protective antibodies in response to the vaccine was lower compared with healthy controls. However, the incidence of illness was similar in both groups. Post vaccination renal function remained stable, and there were no cases of acute rejection after vaccination.

Immunizations against tetanus, literature for patients with CKD is limited. Girndt et al vaccinated seronegative patients with chronic renal failure not on dialysis, patients on long-term haemodialysis, patients after kidney transplantation and compared them with healthy controls. Only 55% of patients in the chronic renal failure group and 69% of patients in the dialysis group reached protective antibody levels. Kidney transplant recipients showed normal seroconversion rates, but lower overall antibody titres. More recently, Kruger et al showed similar findings, with 65% of dialysis patients remaining protected at 1 year. After 5 years, 71% of patients in that study maintained protective antibody levels. The increase in over all protection rate after 5 years occurred because significantly more patients died in the initial non-responder group. Guerin et al found much greater rates of protective antibody levels in 66 haemodialysis patients, with 95.6% of patients achieving protective levels after a booster dose. However, antibody titres decreased rapidly, with only 68% of patients maintaining protective titres after 6 months. In transplant recipients, Huzly et al found much better response rates to tetanus vaccination, with all 150 patients achieving protective antibody levels. Antibody levels, although decreased, remained protective in all patients 12 months after vaccination.

Patients on dialysis show an impaired response to diphtheria vaccination, with a seroconversion rate of only 37%; 33% of patients retain protective levels 5 years after booster administration. Transplant recipients may have an adequate response to booster administration, with protection rates as high as 89% to 95%, but with a rapid decrease in antibody levels within the first year. Other investigators found lower rates of protection in transplant recipients after a diphtheria booster. There were no episodes of acute rejection or decreased graft function associated with tetanus or diphtheria vaccination.

There is very little information on the efficacy and long-term response of hepatitis A vaccines in patients requiring dialysis. These patients are at increased risk for developing severe hepatitis. Fleischmann et al vaccinated 43 consecutive dialysis patients with the Havrix vaccine. Thirty patients received vaccination on a nondialysis day intramuscularly (group A), and 13 patients received vaccination on the day of dialysis subcutaneously (group B). The 30 patients in group A and 12 of 13 patients in group B developed protective antibodies. There were no adverse events in either group. Responses in both groups were similar to those in healthy individuals. However, there was no long-term follow up to evaluate the duration of immunity in these patients. The response to HAV vaccination in haemodialysis patients appears to be similar to that in patients after liver transplantation and greater than that in renal transplant recipients. After 2 doses of the vaccine, 72% of renal transplant recipients developed protective antibody levels.

The incidence of varicella in the transplant population decreased from 45% to 12% after the introduction of immunization. Webb et al immunized 32 children with advanced renal disease (25 children
Table 3
Vaccinations for Patients with CKD Not on Renal Replacement Therapy

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Administration and Schedule</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B</td>
<td>For patients with stage 5 CKD</td>
<td>Not routinely recommended; consider for patients at high likelihood for progression to ESRD</td>
</tr>
<tr>
<td>Influenza</td>
<td>0.5 mL IM annually, preferably in October or November</td>
<td>Can be administered at the same time of pneumococcal vaccine</td>
</tr>
<tr>
<td>S Pneumoniae</td>
<td>0.5 mL SC or IM</td>
<td>Revaccination recommended 5 y after first dose</td>
</tr>
<tr>
<td>Tetanus toxoid</td>
<td></td>
<td>Administer booster every 10 y and after Penetrating wound if last administration &gt; 5 y</td>
</tr>
<tr>
<td>Varicella vaccine</td>
<td>0.5 mL (min, 1,350 PFU) SC; second dose of 0.5 mL 4-8 weeks later</td>
<td>Consider for patients awaiting renal transplantation; may be beneficial in zoster prevention if administered before transplantation</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>1 mL of Havrix or Vaqta IM into the deltoid</td>
<td>Not routinely recommended; for selected populations only</td>
</tr>
</tbody>
</table>

Abbreviations: IM, intramuscular; SC, subcutaneous.

on dialysis and 7 children with a glomerular filtration rate < 20 mL/min/1.73m² [<0.33 mL/s/1.73m²] with no previous history of varicella. Two doses (2,000 PFU) of live attenuated varicella vaccine were administered 3 months apart. All children experienced seroconversion, and the incidence of side effects was low. Of 28 survivors administered 2 doses of vaccine, 82% had protective antibody titres at the time of transplantation, and of the 3 children who subsequently lost their protective titers, 2 children had immunity for the first 12 months after engraftment, when immunosuppressive therapy was the greatest. There were no episodes of varicella infection despite a number of well-documented episodes of exposure to wild type varicella zoster virus. A retrospective analysis of solid organ transplantations performed between 1994 and 1999 at the University of Alberta reported a 7.4% incidence of herpes zoster after renal transplantation; infection caused by herpes zoster was associated with significant morbidity in the form of post herpetic neuralgia (42.7%) and cutaneous scarring (18.7%). An interesting finding of this study is that subjects who developed zoster pretransplantation experienced no recurrence after transplantation. A prospective trial of adult patients is needed to examine the utility of pretransplantation administration of varicella vaccine on the incidence and morbidity of herpes-zoster. The use of varicella vaccine in patients after renal transplantation remains controversial and is not recommended at this time. Hata et al, in a randomised controlled trial, immunized 53 bone marrow transplant recipients who were seropositive for varicella zoster with live attenuated vaccine 30 days before and 30, 60, and 90 days after transplantation. Risk for zoster was 13% in vaccinated patients compared with 33% in controls.

At this time, there are insufficient data to recommend administration of S aureus vaccine to patients on renal replacement therapy. Although Staph VAX vaccine appears to be safe and may have some efficacy over a limited period additional studies are needed and are underway to investigate potential prolongation of the protective effect with booster doses of the vaccine.

CONCLUSION

Vaccines remain an underused tool for the prevention of infectious complications in patients with renal disease. Nephrologists frequently serve as primary care physicians for their patients and thus need to be familiar with the data for commonly used adult vaccinations. Although patients with renal disease may have an impaired immunologic response, successful vaccination of this patient population is possible and can decrease the risk for complications from vaccine preventable diseases. Recent data suggest an association between influenza vaccination and decreased cardiac mortality. Given the markedly increased risk for cardiovascular events in patients with renal disease after pneumococcal vaccination also are needed. The use of varicella vaccine before renal transplantation as a means of decreasing the incidence and morbidity of herpes zoster is of interest.