

Post-transplant Infections

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Although the rates are markedly decreased from previous decades, infection is the most important cause of early morbidity and mortality following transplantation. Infection is closely linked to the degree of immunosuppression and thus to the frequency and intensity of rejection and its therapy. The potential sources of infection in the transplant patient are multiple, including organisms from the allograft itself and from the environment. Patients should be advised to be sensible to possible exposures and to wash their hands thoroughly when exposed to infected individuals or human excrement, specifically, exposures in daycare and occupational settings as well as during gardening and pet care. In those taking immunosuppressive agents, signs and symptoms of infections are frequently blunted until disease is far advanced. Therefore, due to the unusual nature of the infections and the lack of timely symptom development, the key to patient survival is the prevention of infection. Infections may be prevented by pretransplant vaccinations, along with prophylactic medications, preemptive monitoring and behavior modification.

Currently, the most common infectious problems within the first month following transplantation are bacterial infections of the wound, lines, and lungs. Additionally, herpetic stomatitis is common. Beyond 1 month following transplantation, infections are related to more intense immunosuppression and include viral, fungal, protozoal, and unusual bacterial infections. Although hepatitis may occasionally cause fulminate and fatal disease if acquired peritransplantation, the manifestations of hepatitis B or hepatitis C infections occur years following transplantation.

CHAPTER

10

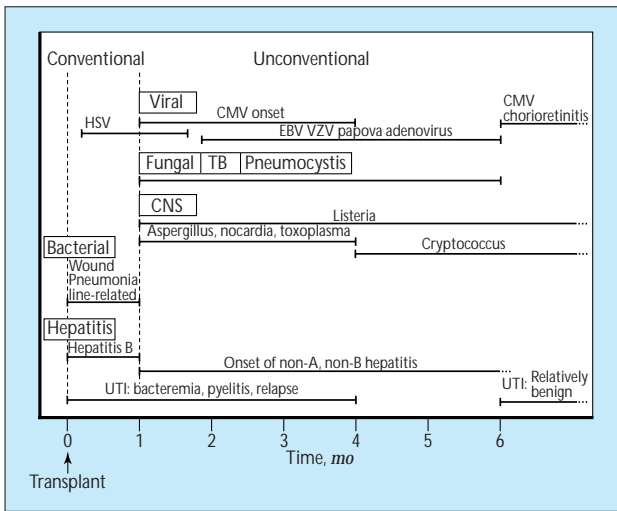


FIGURE 10-1
 Timetable for the occurrence of infection in the renal transplant patient. Exceptions to this chronology are frequent. CMV—cytomegalovirus; CNS—central nervous system; EBV—Epstein-Barr virus; HSV—herpes simplex virus; UTI—urinary tract infection; VZV—varicella-zoster virus. (Adapted from Rubin and coworkers. [1]; with permission.)

CLASSIFICATION OF INFECTIONS OCCURRING IN TRANSPLANT PATIENTS

Infections related to technical complications*

Transplantation of a contaminated allograft, anastomotic leak or stenosis, wound hematoma, intravenous line contamination, iatrogenic damage to the skin, mismanagement of endotracheal tube leading to aspiration, infection related to biliary, urinary, and drainage catheters

Infections related to excessive nosocomial hazard

Aspergillus species, *Legionella* species, *Pseudomonas aeruginosa*, and other gram-negative bacilli, *Nocardia asteroides*

Infections related to particular exposures within the community

Systemic mycotic infections in certain geographic areas
Histoplasma capsulatum, *Coccidioides immitis*, *Blastomyces dermatitidis*, *Strongyloides stercoralis*

Community-acquired opportunistic infection resulting from ubiquitous saprophytes in the environment†

Cryptococcus neoformans, *Aspergillus* species, *Nocardia asteroides*, *Pneumocystis carinii*

Respiratory infections circulating in the community

Mycobacterium tuberculosis, influenza, adenoviruses, parainfluenza, respiratory syncytial virus

Infections acquired by the ingestion of contaminated food/water

Salmonella species, *Listeria monocytogenes*

Viral infections of particular importance in transplant patients

Herpes group viruses, hepatitis viruses, papillomavirus, HIV

*All lead to infection with gram-negative bacilli, *Staphylococcus* species, and/or *Candida* species.

†The incidence and severity of these infections and, to a lesser extent, the other infections listed, are related to the net state of immunosuppression present in a particular patient.

FIGURE 10-2
 Classifications of infections occurring in transplant patients. (Adapted from Rubin [2]; with permission.)

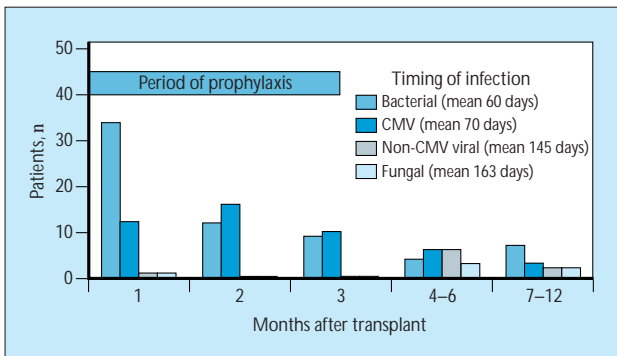


FIGURE 10-3
 Timing of infections following kidney/pancreas transplantation at a single transplantation center using antiviral (ganciclovir IV followed by acyclovir) and antibacterial (trimethoprim-sulfamethoxazole) prophylaxis. CMV—cytomegalovirus. (From Stratta [3]; with permission.)

Preventive Strategies

INFECTIOUS DISEASE HISTORY TO BE TAKEN PRIOR TO TRANSPLANTATION

1. Past immunizations.
2. Past infections or exposures to infections.
 - A. Bacterial
Rheumatic fever, sinusitis, ear infections, urinary tract infections, pyelonephritis, pneumonia, diverticulitis, tuberculosis
 - B. Viral
Measles, mumps, varicella, rubella, hepatitis
3. Chronic or recurrent infections, such as pneumonia, sinusitis, urinary tract infection, or diverticulitis
4. Surgical history, such as splenectomy
5. Transfusion or previous transplant history and dates
6. Past travel history, including military service
7. Past immunosuppressive drug treatment (eg, for asthma, renal disease, or rheumatologic disease)
8. Lifestyle
 - A. Smoking, drinking, illicit drug use, marijuana smoking
 - B. Sexual partners, orientation, unprotected contact and date, safety practices used, sexually transmitted diseases, genital warts
 - C. Food, consumption of raw fish or meat, consumption of unpasteurized products, such as milk, cheese, fruit juices, or tofu
 - D. Avocation—gardening and the use of gloves, cleaning sheds, hiking, camping, water sources, bathing pets, cleaning pet litter and cages, hunting practices
 - E. Vocation—jobs that require exposure to possible infectious agents, such as daycare, ministry, small closed offices, garbage collections or dump workers, construction workers, forestry workers, health care, veterinarians, farmers

FIGURE 10-4

Infectious disease history to be taken prior to transplantation.

PRETRANSPLANT VACCINATIONS OR BOOSTERS TO BE GIVEN TO ALL TRANSPLANT RECIPIENTS UNLESS RECENT ADMINISTRATION CAN BE DOCUMENTED

1. Td (Tetanus toxoid, diphtheria)
2. Pneumococcal vaccine
3. Hepatitis B
4. Influenza

FIGURE 10-5

Pretransplant vaccinations or boosters to be given to all transplant recipients unless recent administration can be documented.

PRETRANSPLANT VACCINATIONS TO BE GIVEN IF SERONEGATIVE OR PAST INFECTION BY HISTORY CANNOT BE DOCUMENTED

1. Measles-mumps-rubella vaccine
2. Polio
3. Varicella (0.5 mL subcutaneously followed by booster of 0.5 mL in 4–8 weeks)
4. *Haemophilus influenzae* type B

FIGURE 10-6

Pretransplant vaccinations to be given if seronegative or past infection by history cannot be documented.

INACTIVATED VACCINES THAT ARE CONSIDERED SAFE AND MAY BE GIVEN AS NEEDED POST-TRANSPLANT FOR ANTICIPATED EXPOSURE

1. Anthrax
2. Cholera
3. Rabies vaccine absorbed
4. Human diploid cell rabies vaccine
5. Inactivated typhoid vaccine, capsular polysaccharide parenteral vaccine, or heat phenol-treated parenteral vaccine
6. Japanese encephalitis virus vaccine
7. Meningococcal vaccine
8. Plague vaccine

VACCINES THAT MAY NOT BE GIVEN (LIVE ATTENUATED VACCINES)

1. Bacille Calmette-Guérin (BCG)
2. Measles
3. Mumps
4. Rubella
5. Oral polio
6. Oral typhoid
7. Yellow fever

FIGURE 10-8

Vaccines that may not be given include live attenuated vaccines.

FIGURE 10-7

Inactivated vaccines that are considered safe and may be given as needed post-transplant for anticipated exposure.

A. DOSAGE AND ADMINISTRATION GUIDELINES FOR VACCINES AVAILABLE IN THE UNITED STATES

Vaccine	Dosage	Route of administration	Type
DT	0.5 mL	IM	Toxoids
Td	0.5 mL	IM	Toxoids
DTP	0.5 mL	IM	Diphtheria and tetanus toxoids with killed <i>B. pertussis</i> organisms
DTaP (Acel-Imune)	0.5 mL	IM	Diphtheria and tetanus toxoids with acellular pertussis
DTP-HbOC (Tetramune)	0.5 mL	IM	Diphtheria and tetanus toxoids with killed <i>B. pertussis</i> organisms and <i>Haemophilus b</i> conjugate (diphtheria CRM ₁₉₇ protein conjugate)
<i>Haemophilus B</i> , conjugate vaccine	0.5 mL	IM	
ProHIBit (PRP-D), manufactured by Connaught Laboratories	0.5 mL	IM	Polysaccharide (diphtheria toxoid conjugate)
HibTITER (HbOC), manufactured by Praxis Biologicals	0.5 mL	IM	Oligosaccharide (diphtheria CRM protein conjugate)
PedvaxHib (PRP-OMP), manufactured by MSD	0.5 mL	IM	Polysaccharide (meningococcal protein conjugate)
Hepatitis B		IM in the anterolateral thigh or in the upper arm; SC in individuals at risk of hemorrhage	Yeast recombinant-derived inactivated viral antigen
Infants born to HB _e Ag-negative mothers and children < y[]			
Recombivax HB (MSD)	2.5 µg (0.25 mL)		
Engerix-B (SKF)	10 µg (0.5 mL)		

FIGURE 10-9

A–D, General immunization guidelines. HBOC—haemophilus *B* influenzae–diphtheria protein conjugate vaccine, oligosaccharide; ID—intradermal; IM—intramuscularly; DT—diphtheria tetanus; DTP—diphtheria tetanus pertussis; MMR—measles mumps rubella; MR—measles rubella; MSD—Merck Sharpe & Dohme;

PRP-D—haemophilus *B*–diphtheria toxoid conjugate vaccine, polysaccharide; PRP-OMP—haemophilus influenzae type b–meningococcal protein conjugate vaccine; SC—subcutaneous; SKF—SmithKline and French; Td—tetanus, diphtheria. (From Isada and coworkers [4]; with permission.)

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B. DOSAGE AND ADMINISTRATION GUIDELINES FOR VACCINES AVAILABLE IN THE UNITED STATES

Infants born to HB_eAg-positive mothers (immunization and administration of 0.5 mL hepatitis B immune globulin is recommended for infants born to HB_eAg mothers using different administration sites) within 12 hours of birth; administer vaccine at birth; repeat vaccine dose at 1 and 6 months following the initial dose

Vaccine	Dosage
Recombivax HB (MSD)	5 µg (0.5 mL)
Engerix-B (SKF)	10 µg (0.5 mL)
Children 11–19 y	
Recombivax HB (MSD)	5 µg (0.5 mL)
Engerix-B (SKF)	20 µg (1 mL)
Adults > 19 y	
Recombivax HB (MSD)	10 µg (1 mL)
Engerix-B (SKF)	20 µg (1 mL)
Dialysis patients and immunosuppressed patients	
Recombivax HB (MSD)	<11 y, 20 µg (0.5 mL); ≥11 y, 40 µg, (1 mL) using special dialysis formulation
Engerix-B (SKF)	<11 y, 20 µg (1 mL); ≥11 y, 40 µg (2 mL), give as two 1 mL doses at different sites

C. DOSAGE AND ADMINISTRATION GUIDELINES FOR VACCINES AVAILABLE IN THE UNITED STATES

Vaccine	Dosage	Route of administration	Type
Influenza		IM (2 doses 4+ weeks apart in children <9 years of age not previously immunized; only 1 dose needed for annual updates)	Inactivated virus subvirion (split) (contraindicated in patients allergic to chicken eggs)
Split virus only in pediatric patients			
6–35 mo	0.25 mL (1 or 2 doses)		
3–8 y	0.5 mL (1 or 2 doses)		
≥9 y	0.5 mL (1 dose)		
Measles	0.5 mL	SC	Live virus (contraindicated in patients with anaphylactic allergy to neomycin)

Most areas: Two doses (1st dose at 12 months with MMR; 2nd dose at 4–6 years or 11–12 years, depending on local school entry requirements).
 High-risk area: Two doses (1st dose at 12 months with MMR; 2nd dose as above).
 Children 6–15 months in epidemic situations: Dose is given at the time of first contact with a health care provider; children <1 year of age should receive single antigen measles vaccine. If vaccinated before 1 year, revaccinate at 15 months with MMR. A 3rd dose is administered at 4–6 years or 11–12 years, depending on local school entry requirements.

FIGURE 10-9 (Continued)

(Continued on next page)

D. DOSAGE AND ADMINISTRATION GUIDELINES FOR VACCINES AVAILABLE IN THE UNITED STATES

Children 6–15 months in epidemic situations: Dose is given at the time of first contact with a health care provider; children <1 year of age should receive single antigen measles vaccine. If vaccinated before 1 year, revaccinate at 15 months with MMR. A 3rd dose is administered at 4–6 years or 11–12 years, depending on local school entry requirements.

Vaccine	Dosage, mL	Route of administration	Type
Meningococcal	0.5	SC	Polysaccharide
MMR	0.5	SC	Live virus
MR	0.5	SC	Live virus
Mumps	0.5	SC	Live virus
Pneumococcal polyvalent	0.5 (≥2 y)	IM or SC (IM preferred)	Polysaccharide
Poliovirus (OPV) trivalent	0.5	Oral	Live virus
Poliovirus (IPV) trivalent	0.5	SC	Inactivated virus
Rabies	1	IM ^{††} , ID ^{§§}	Inactivated virus
Rubella	0.5 (≥12mo)	SC	Live virus
Tetanus (adsorbed)	0.5	IM	Toxoid
Tetanus (fluid)	0.5	IM, SC	Toxoid
Yellow fever	0.5	SC	Live attenuated virus

FIGURE 10-9 (Continued)

PRETRANSPLANT VIRAL SEROLOGIES TO CHECK AT THE PRETRANSPLANT VISIT

Viral serology	Treatment, work-up modification or change in post-transplant treatment
Herpes simplex virus 1, 2	If positive, treat early post-transplant with acyclovir, famciclovir, or ganciclovir
Epstein-Barr virus	If negative, consider post-transplant ganciclovir. Test donor due to risk of post-transplant lymphoma with primary infection
Varicella-zoster virus	Consider vaccination with Oka strain live attenuated virus if negative or treatment with acyclovir following clinical exposure
Cytomegalovirus	If the recipient is positive or donor positive, consider prophylactic or preemptive antiviral treatment
HBeAg	If positive, check HBeAg and HBDNA and biopsy. If HBDNA positive, consider pretransplant antiviral treatment with interferon if biopsy allows. Consult hepatologist regarding other treatment options
Hepatitis C virus	If positive, check HCV RNA status by polymerase chain reaction. If positive biopsy even with normal transaminase values and consider pretransplant treatment with interferon
HIV	Consider safety of transplantation if true positive. More data are required to make an informed decision

FIGURE 10-10

Pretransplant viral serologies to check at the pretransplant visit.

PRETRANSPLANT BACTERIAL SEROLOGIES

Serology	Modification
RPR (Rapid plasma reagin)	If positive, check with a treponemal specific test—Fluorescent treponemal antibody absorbed test (FTA-ABS) or microhemagglutination assay for treponema pallidum (MHA-TP)
PPD	If positive the general recommendation without documented previous treatment after first evaluating a chest radiograph is isoniazid 300 mg/d to continue for 6 months or 9 to 12 months post-transplant

FIGURE 10-11

Pretransplant bacterial serologies.

EFFECT AND POSSIBLE EFFECTS OF PROPHYLACTIC ANTIVIRAL STRATEGIES

No treatment	Acyclovir orally × 3M	Ganciclovir IV acyclovir PO × 3M	CMVlgG × 5 doses	Ganciclovir × 3M PO
Risk: ↑ HSV	↓ HSV	↓ HSV	? Effect	↓ HSV
↑ CMV	Slight ↓ CMV	Slight ↓ CMV	Slight ↓ CMV	↓ CMV
↑ VZV	↓ VZV	↓ VZV	? Effect	↓ VZV
↑ EBV	Slight ↓ EBV	↓ EBV	? Effect	↓ EBV
↑ Adenovirus	No change in adenovirus	? Adenovirus	? Effect	? Slight ↓ in adenovirus
↑ HHV6	Slight ↓ HHV6	Slight ↓ HHV6	? Effect	? ↓ HHV6
↑ HHV8	Slight ↓ HHV8	Slight ↓ HHV8	? Effect	? ↓ HHV8

FIGURE 10-12

Effect and possible effects of prophylactic antiviral strategies. CMV—cytomegalovirus; EBV—Epstein-Barr virus; HHV6—human herpes

virus 6; HHV8—human herpes virus 8; HSV—herpes simplex; VZV—varicella zoster. *Question mark* indicates question as to the effect.

PROPHYLACTIC ANTIBACTERIAL AND ANTIPROTOZOAL STRATEGIES

Type of infection	Treatment perioperatively or postoperatively
Wound	Against uropathogens and staphylococci, eg, ampicillin-sulbactam, cefazolin plus aztreonam × 24 to 48 hours adjusted for renal function
Urinary tract	Risk ↑ urinary leak, hematoma, lymphocele Common choices Trimethoprim sulfamethoxazole Ciprofloxacin Cephazolin Ampicillin Duration of treatment varies An important factor is the presence of the urinary catheter
<i>Legionella</i>	Trimethoprim sulfamethoxazole
Pneumocystis	Trimethoprim sulfamethoxazole
Toxoplasmosis	Trimethoprim sulfamethoxazole
Nocardia	Trimethoprim sulfamethoxazole
<i>Listeria monocytogenes</i>	Trimethoprim sulfamethoxazole

FIGURE 10-13

Prophylactic antibacterial/antiprotozoal strategies.

Prevention Strategies

PREVENTION OF RESPIRATORY INFECTIONS IN THE IMMUNOSUPPRESSED PATIENT

Infection	Options for prevention
Pneumococcal pneumonia	Pneumococcal vaccination; oral penicillin prophylaxis; passive prophylaxis with immune globulin
Influenza illness	Annual influenza vaccination; amantadine or rimantadine prophylaxis (for influenza A virus only)
<i>Haemophilus influenzae</i>	<i>H. influenzae</i> type B vaccination
Tuberculosis	Case finding and early treatment; infection control procedures; preventive therapy with isoniazid
<i>Mycobacterium avium</i> complex illness	Rifabutin prophylaxis
<i>Pneumocystis carinii</i> pneumonia	Prophylaxis with oral trimethoprim-sulfamethoxazole or aerosolized pentamidine
CMV pneumonia	Use of CMV-seronegative organs and blood products for CMV-seronegative recipients; passive prophylaxis with CMV immune globulin; prophylaxis with antiviral agents (acyclovir, ganciclovir)
<i>Legionella</i> pneumonia	Identification of source; institution of control measures associated with potable water, such as hyperchlorination, maintenance of hot water temperature above 50°C (122°F)
Aspergillosis	Use of HEPA filter to minimize airborne spores; avoidance of decaying leaves and vegetation
<i>Candida</i> illness	Prophylaxis with antifungal agents
Cryptococcosis	Avoidance of pigeons and pigeon droppings; prophylaxis with antifungal agents
Histoplasmosis	Complete travel history to identify patients at risk; avoidance of areas of high exposure to <i>Histoplasma</i> ; formalin treatment of infected soil
Coccidioidomycosis	Complete travel history to identify patients at risk; avoidance of areas of high exposure to <i>Coccidioides immitis</i>
Strongyloidiasis	Complete travel history to identify patients at risk; ova and parasite analysis of stool specimen in patients at risk; thiabendazole prophylaxis

FIGURE 10-14

Prevention strategies for the prevention of pulmonary infection. CMV—cytomegalovirus; HEPA—high-efficiency particulate air. (Adapted from Maguire and Wormser [5]; with permission.)

PASSIVE IMMUNIZATION AGENTS—IMMUNE GLOBULINS

Immune globulin	Dosage	Route
Hepatitis B (H-BIG*)		IM
Percutaneous inoculation	0.06 mL/kg/dose (within 24 h) (5 mL max)	
Perinatal	0.5 mL/dose (within 12 h of birth)	
Sexual exposure	0.06 mL/kg/dose (within 14 d of contact) (5 mL max)	
Immune globulin (IG)		IM*
Hepatitis A prophylaxis	0.02 mL/kg/dose (as soon as possible or within 2 wk after exposure) (single exposure)	
	0.06 mL/kg/dose (>3 mo or continuous exposure) repeat every 4–6 mo	
Hepatitis B	0.06 mL/kg/dose (H-BIG should be used)	
Hepatitis C	0.06 mL/kg/dose (percutaneous exposure)	
Measles†	0.25 mL/kg/dose (max 15 mL/dose) (within 6 d of exposure)	
	0.5 mL/kg/dose (max 15 mL/dose) (immunocompromised children)	
Rabies‡	20 IU/kg/dose (within 3 d)	
Tetanus (serious, contaminated, wounds; <3 previous tetanus vaccine doses)	250–500 units/dose	IM
Varicella-zoster §(VZIG)	Within 48 hours but not later than 96 hours after exposure	IM ¶
	0–10 kg 125 units = 1 vial	
	10.1–20 kg 250 units = 2 vials	
	20.1–30 kg 375 units = 3 vials	
	30.1–40 kg 500 units = 4 vials	
	>40 kg 625 units = 5 vials	

*Deep IM in the gluteal region for large doses only. Deltoid muscle or the anterolateral aspect of the thigh are preferred sites for injection. No greater than 5 mL/site in adults or large children; 1–3 mL/site in small children and infants. Maximum dose: 20 mL at one time.

†IG prophylaxis may not be indicated in a patient who has received IGIV within 3 weeks of exposure.

‡1/2 of dose used to infiltrate the wound with the remaining 1/2 of dose given IM Rabies immune globulin is not recommended in previously HDCV immunized patients.

§No greater than 2.5 mL of VZIG/one injection site. Doses >2.5 mL should be divided and administered at different sites.

FIGURE 10-15

Passive immunization agents for prevention postexposure. HBIG—hepatitis B immune globulin; HDCV—human diploid cell rabies vaccine; IG—immune globulin; IGIV—intravenous

immune globulin; IM—intramuscularly; VZIG—varicella zoster immune globulin. (From Isada and coworkers [4]; with permission.)

GUIDELINES FOR SPACING THE ADMINISTRATION OF IMMUNE GLOBULIN (IG) PREPARATIONS AND VACCINES

Immunobiologic combinations		Recommended minimum interval between doses
Simultaneous administration		
IG and killed antigen		None. May be given simultaneously at different sites or at any time between doses.
IG and live antigen		Should generally not be given simultaneously. If unavoidable to do so, give at different sites and revaccinate or test for seroconversion in 3 months. Example: MMR should not be given to patients who have received immune globulin within the previous 3 months.
Nonsimultaneous administration		
First	Second	
IG	Killed antigen	None
Killed antigen	IG	None
IG	Live antigen	6 wk, and preferably 3 mo
Live antigen	IG	2 wk

*The live virus vaccines, OPV, and yellow fever are exceptions to these recommendations. Either vaccine may be administered simultaneously or any time before or after IG without significantly decreasing antibody response.

FIGURE 10-16

Live virus vaccinations generally not given to transplant patients. IG—immune globulin; OPV—poliovirus vaccine live oral. (From Isada and coworkers [4]; with permission.)

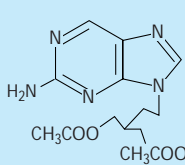
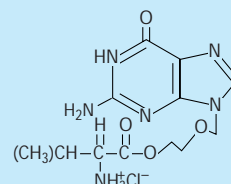
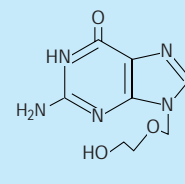
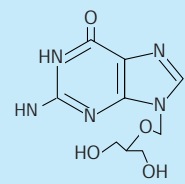
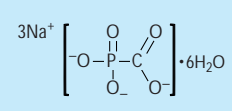
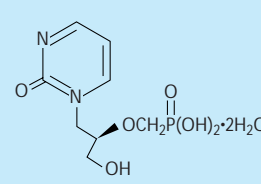
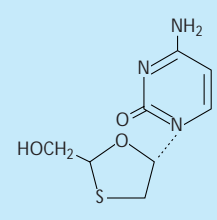
				
	Famciclovir → Penciclovir	Valacyclovir → Acyclovir	Acyclovir	Ganciclovir
Oral bioavailability:	77%	54%	15%	2%–7%
Excretion:	100%* R	100% liver/GI	100%* R	91% unchanged urine
Plasma t1/2:	2–3 h	2–3 h	2–3 h	2–3 h
Intracellular t1/2:	7–20 h	0.7–1 h	0.7–1 h	6 h–3 wk
Antiviral spectrum:	HSV/V2V/EBV	HSV/V2V/EBV	HSV/V2V/EBV	HHV8, CMV, adeno, HBV
A				
				
	Phosphonoformic acid Foscarnet	Cidofovir	Lamivudine	
Administration:	IV	IV	86% oral bioavailability	
t1/2:	2–6 h	3–4 h	5–7 h	
Tissue t1/2:	87.5±41.8 h	17–65 h	10–15 h	
Metabolism:	100% renal excretion	85% renal excretion	70%–90% renal excretion	
B				

FIGURE 10-17

Antiviral agents. *Asterisk* indicates excreted unchanged in the urine; all antivirals are subject to changes in t1/2 with changing renal function. Adeno—adenovirus;

CMV—cytomegalovirus; EBV—Epstein-Barr virus; HHV8—human herpesvirus 8; HSV—herpes simplex virus; VZV—varicella-zoster virus.

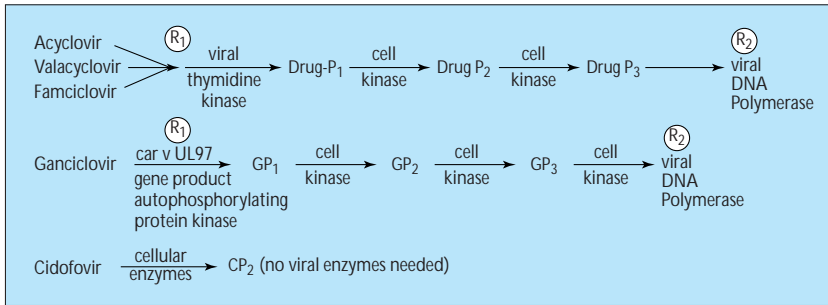


FIGURE 10-18

Antiviral activation and action (acyclovir, valacyclovir, famciclovir, ganciclovir). Resistance (R) to antivirals has been found at the level of viral thymidine kinase (R1) and DNA polymerase (R2). Ganciclovir is monophosphorylated in cytomegalovirus (CMV)-infected cells by the CMV UL97 gene product. Acyclovir, valacyclovir, and famciclovir are not easily phosphorylated in CMV-infected cells. Cidofovir does not require viral enzymes to be phosphorylated to the active diphosphate.

DRUG INTERACTIONS BETWEEN ANTIVIRALS, ANTIFUNGALS, ANTIBACTERIALS, ANTIMYCOBACTERIALS, AND ANTIPROTOZOALS WITH CYCLOSPORINE AND FK506

Drug	Effect on CSA/FK506	Nephrotoxicity of combination
Antifungals		
Amphotericin B		↑↑
Clotrimazole troches (more in FK506)	↑	↑
Ketoconazole (keto>itra>fluconazole)	↑↑	
Griseofulvin	↓	
Antibacterial		
Clarithromycin	↑	↑
Doxycycline	↑	
Erythromycin	↑↑	
Gentamicin		↑
Nafcillin	↓	
Rifampin	↓↓	
Rifabutin	↓↓	
Sulfamethoxazole/trimethoprim	↓	↑
Ticarcillin	↑	
Antimycobacterial		
Isoniazid	↓	
Pyrazinamide	↓	
Antiparasitic		
Chloroquine	↑	

FIGURE 10-19

Drug interactions between antivirals, antifungals, antibacterials, antimycobacterials, and antiprotozoals with cyclosporine and FK506. (From Lake [6] and Yee [7]; with permission.)

INFECTIONS TRANSMITTED TO TRANSPLANT RECIPIENTS VIA THE DONOR ORGAN

Virus	Bacteria	Fungi	Parasitic
HIV, cytomegalovirus, herpes simplex virus, Epstein-Barr virus, hepatitis B virus, hepatitis C virus, hepatitis D virus, ? hepatitis G virus, adenovirus (?), parvovirus (?), papillomavirus, rabies, Creutzfeldt-Jakob	Aerobe (gram positive), aerobe (gram negative), anaerobes, <i>Mycobacterium tuberculosis</i> , atypical mycobacteria	<i>Candida albicans</i> , <i>Histoplasma capsulatum</i> , <i>Cryptococcus neoformans</i> , <i>Marosporium apiospermum</i>	Malaria toxoplasmosis, trypanosomiasis, strongyloidiasis

FIGURE 10-20

Infections transmitted to transplant recipients via the donor organ.

Cytomegalovirus

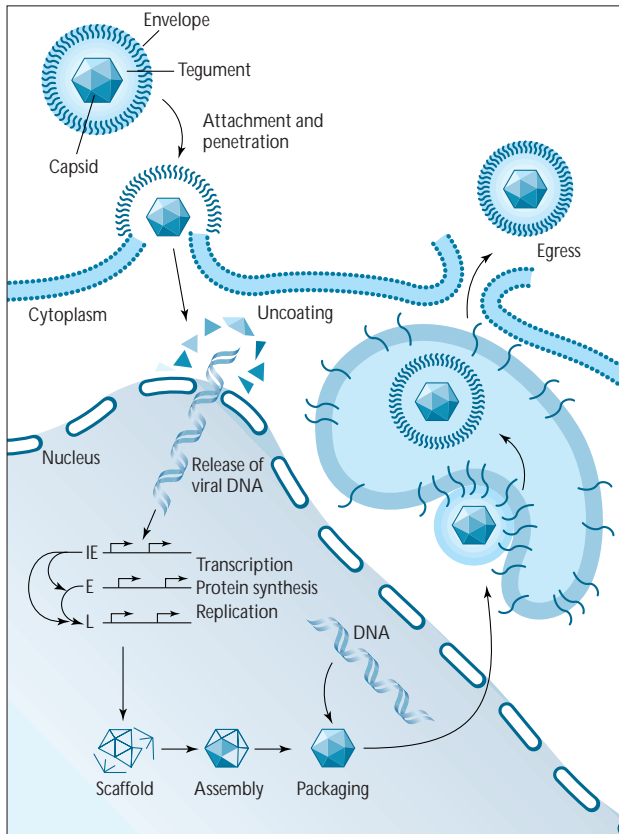


FIGURE 10-21

The lifecycle of cytomegalovirus (CMV). The envelope binds with the cell membrane, and the DNA is uncoated and transferred into the nucleus, where cell protein synthesis machinery is used to manufacture new DNA and capsid. The DNA is packaged into the capsid and returns to the cytoplasm, where the tegument and envelope are assembled around the capsid and the whole virus transported to the cellular surface and released.

CMV is a double-stranded DNA virus that causes disease following transplantation after primary infection, reinfection, or reactivation of latent infections. CMV disease is seen most frequently within the first 4 to 6 months of transplantation if no antiviral prophylaxis is used; however, in the presence of antiviral prophylaxis and new immunosuppressive agents, the onset of CMV disease may be shifted to longer intervals from transplantation. There also may be a slight increase in the occurrence of CMV enteritis with the use of some of the newer combinations of immunosuppressive agents. When the recipient is CMV positive and receives an organ from a CMV-positive donor, reactivation of the latent infection in the recipient is responsible for 15% to 30% of the infections seen, and reinfection with the virus from the donor is responsible for 70%.

CMV disease prevention may be accomplished by administering prophylactic antiviral agents or by the use of routine surveillance testing. Variables to be considered in an individual's risk of CMV disease development are the use of antilymphocyte medications, and the donor and recipient, CMV serostatus. The highest risk group for CMV disease is the group at risk for primary CMV exposure and those given antilymphocyte preparations. Specifically, increased CMV disease is seen during situations that trigger viral replication. High levels of tumor necrosis factor alpha, such as levels occurring during infections or after OKT3 administration, activate the CMV promoter, thus stimulating the conversion from the latent to the reactivated state.

All of the prophylactic strategies for the prevention of CMV disease have shown some benefit in different studies; currently, however, the most effective approach is oral ganciclovir. A more bioavailable oral ganciclovir may even increase the effectiveness and is now under investigation. Oral ganciclovir is started when the patient is able to take oral medications within the first week following transplantation and is administered at a dose of 1 g 3 times a day for 3 months following transplantation adjusted for renal function. The protective effect is also seen in those who have received antilymphocyte preparations. The most desirable solution would be a vaccine that induced natural immunity mechanisms. Vaccines targeted against the structural glycoproteins of CMV are currently continuing under development but are not yet available; their ultimate effectiveness is not known at this time. As patients who already have had natural infections are not immune to reinfection or reactivation, a vaccine solution may not be possible.

MANIFESTATIONS OF CMV DISEASE IN RENAL TRANSPLANT RECIPIENTS

CMV disease

- A. Syndrome: fever, leukopenia, malaise, lack of another cause
- B. Organ specific: hepatitis, enteritis—duodenum, colon; pancreatitis; pneumonitis; interstitial nephritis, retinitis
- C. Risk of CMV disease by donor

Recipient serostatus without antiviral prophylaxis

D/R	Infection*	Disease
D+R-	70%–100%	56%–80%
D+R+	50%–80%	27%–39%
D-R+		0%–27%
D-R-		<5%

*Infection determined by new anti-CMV antibody development or a greater than fourfold rise in anti-CMV titers.

FIGURE 10-22

Manifestations of cytomegalovirus (CMV) disease in renal transplant recipients.

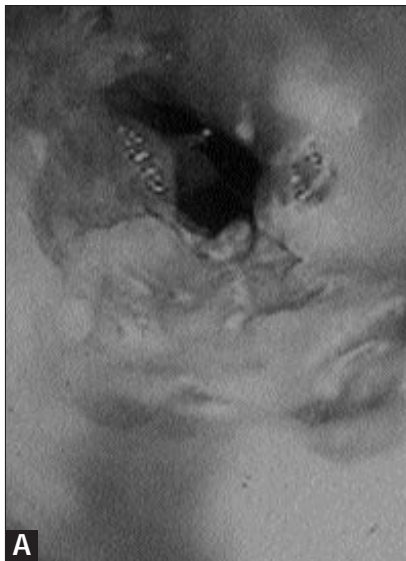


FIGURE 10-23 (see Color Plates)

Endoscopic aspects of cytomegalovirus (CMV) infection. **A**, CMV esophageal ulcers. **B**, CMV duodenal ulcers.

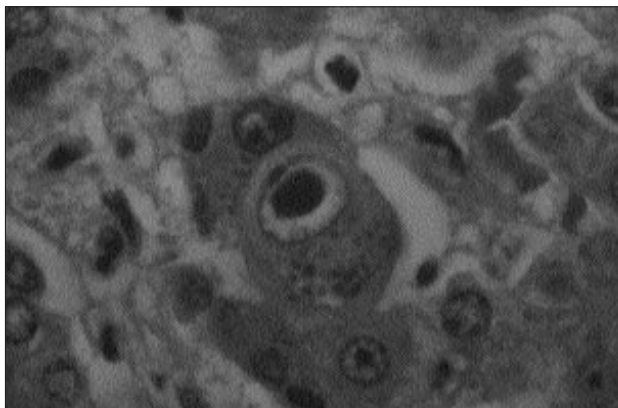


FIGURE 10-24 (see Color Plate)

Histologic lesion in cytomegalovirus infection.

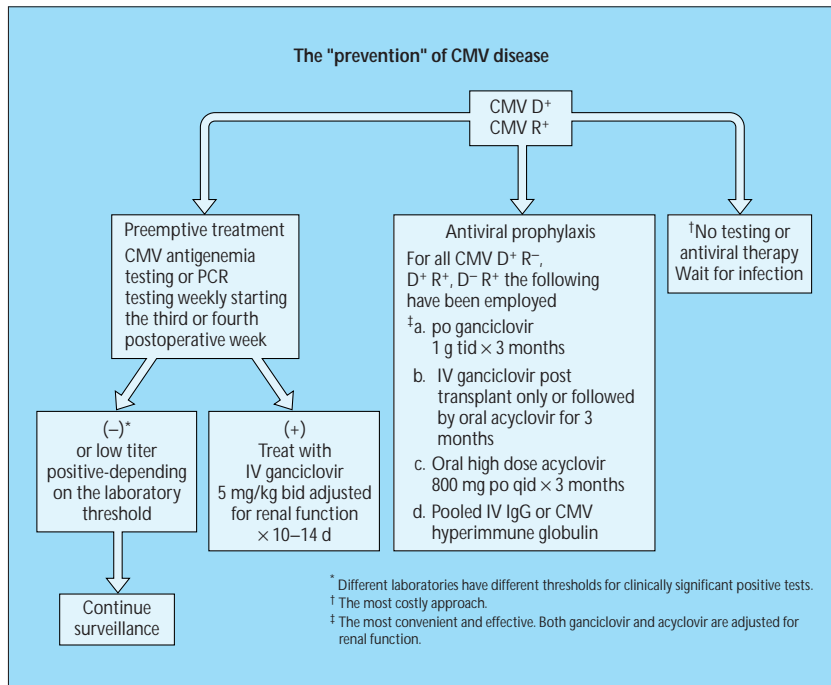
**RANDOMIZED TRIALS EVALUATING CMV PROPHYLACTIC STRATEGIES
ADMINISTERED DURING THE TIME OF GREATEST RISK FOR CMV DISEASE**

Drug	Author	Induction or Rejection Antilymphocyte	Serostatus	Control		Treated		Dosing
				n	CMV Disease	n	CMV Disease	
IgG	Metsellar	ATG-rej	All patients	20	30%	19	37%	Cytotec, 6 doses
	Steinmuller	ALG/OKT3	R+	18	39%	16	13%	Sandoglobulin, 5 doses
	Teuschert	None	D+R-	18	100%	18	20%	Cytotec, 11 doses
	Snydman*	*Some*	D+R-	35	60%	24	21%	Cytotec
	Boland	None	D+R-	11	18%	11	27%	Cytotec, 5 doses
Acyclovir—PO	Balfour	ALG	All patients	51	29%	53	8%	Acyclovir 800 mg po qid x 3 months
			Subgroups					
			D+R-	7	100%	6	17%	
			D+R+	8	38%	9	11%	
Ganciclovir	Rondeau	ATG/OKT3	D+R-	15	73%	17	47%	Ganciclovir 5 mg/kg bid IV d14–28
	Conti	Antilymphocyte	R+	18	56%	22	9%	Ganciclovir with antilymphocyte drug 2.5 mg/kg/IV bid
	Hibberd	OKT3	R+	49	33%	64	14%	Ganciclovir 2.5 mg/kg/d during ALG
	Brennan	ATG	D+or R+	23	61%	19	21%	Oral ganciclovir 1 g tid
Valacyclovir	Squillet	NA	R+	204	10.8%	204	0%	2 g qid

*Antilymphocyte serum was given to two globulin and eight control patients as induction therapy and four globulin and seven control patients as antirejection therapy.

FIGURE 10-25

Randomized trials evaluating cytomegalovirus (CMV) prophylactic strategies administered during the time of greatest risk for CMV disease.

**FIGURE 10-26**

The "prevention" of cytomegalovirus (CMV) disease. This figure shows the different strategies for the management of CMV-positive transplant recipients or recipients of CMV-positive organs.

DETECTION OF CMV DISEASE AND INFECTION

Antibodies: the development of IGM anti-CMV antibodies, a four fold or greater increase in IgG titers

Culture:

- A. Standard culture in a fibroblast monolayer
Results may require up to 6 wk
- B. Shell vial cultures—the buffy coat is centrifuged onto fibroblasts increasing fibroblast infection. Viral infection is detected by applying a monoclonal antibody directed against the 72-Kd major immediate early protein of CMV. RBCs in the buffy coat may be toxic to the monolayer resulting in a false-negative test. Urine and BAL specimens may be positive without predicting disease. Results are available in 16 to 36 h.

Other:

- A. Antigenemia—Granulocytes and monocytes are isolated and stained with a monoclonal antibody against a matrix, tegument protein pp65 (structural late protein). Culture is not required, granulocytes and monocytes from the buffy coat are stained, testing results are available in 4 to 6 h. It may be argued that the positivity may not be due to replicating virus in the WBCs but due to exogenous acquisition from infected endothelial cells. The number of antigen positive cells per unit number of WBC counted that determines the onset of symptomatic diseases depends upon the individual laboratory; however, usually over 10 positive cells per 10^5 WBC precede the onset of symptoms by approximately 1 week.
- B. Polymerase chain reaction—For the detection of CMV DNA in whole blood or serum. CMV DNA is amplified from whole blood or serum. The sensitivity and predictive value depend on the laboratory.

FIGURE 10-27

Detection of cytomegalovirus (CMV) disease and infection. BAL—bronchoalveolar lavage; RBC—red blood cell; WBC—white blood cell.

Tuberculosis

SOME ANTITUBERCULOSIS DRUGS

Drug	Adult dosage (daily)	Pediatric dosage (daily)	Main adverse effects
Primary antituberculous therapy			
Isoniazid ^{††} (<i>LN.H.</i> , and others)	300 mg	10–20 mg/kg (max. 300 mg)	Hepatic toxicity
Rifampin ^{‡‡} (Rifadin, Rimactane)	600 mg	10–20 mg/kg (max. 600 mg)	Hepatic toxicity, flu-like syndrome
Pyrazinamide [§]	15–30 mg/kg	same as adult	Hepatic toxicity, hyperuricemia
Ethambutol [¶] (Myambutol)	15 mg/kg (about 1 g)	same as adult	Optic neuritis
Other Drugs			
Capreomycin (Capastat)	15 mg/kg IM or IV	15–30 mg/kg	Auditory and vestibular toxicity, renal damage
Kanamycin (Kantrex, and others)	15 mg/kg IM ^{††}	15–30 mg/kg	Auditory toxicity, renal damage
Streptomycin ^{**}	250–500 mg bid ^{††}	20–40 mg/kg IM	Vestibular toxicity, renal damage
Cycloserine (Seromycin, and others)	250–500 mg bid	15–20 mg/kg	Psychiatric symptoms, seizures
Ethionamide (Trecator-SC)	500–750 mg bid	15–20 mg/kg	Gastrointestinal and hepatic toxicity
Ciprofloxacin (Cipro)	200–400 mg q12h or	Not recommended	Nausea
Ofloxacin (Floxin)	400–800 mg/day	Not recommended	Nausea

*Rifamate (containing rifampin 300 mg plus isoniazid 150 mg) is also available

[†]Can be given orally or parenterally. Pyridoxine should be given to prevent neuropathy in malnourished or pregnant patients and those with alcoholism or diabetes. For intermittent use after a few weeks to months of daily dosage, the dosage is 15 mg/kg twice/wk (max. 900 mg).

[‡]Available orally or intravenously. For intermittent use after a few weeks to months of daily dosage, the dosage is 600 mg twice/wk.

[§]For intermittent use after a few weeks to months of daily dosage, the dosage is 40–50 mg/kg twice/wk (max. 3 g).

[¶]Daily dosage should be 25 mg/kg/d if organism isoniazid-resistant or during first 1 to 2 months; decrease dosage if renal function diminished. For intermittent use after a few weeks to months of daily dosage, the dosage is 50 mg/kg twice/wk.

^{**}Temporarily not available in the United States.

^{††}For patients > 40 years old, 500 to 750 mg/d or 20 mg/kg twice/wk; decrease dosage if renal function is diminished. Some clinicians change to lower dosage at 60 rather than 40 years of age.

^{‡‡}Some authorities recommend pyridoxine 50 mg for every 250 mg of cycloserine to decrease the incidence of adverse psychiatric effects.

FIGURE 10-28

The treatment of tuberculosis (TB) depends on the clinical presentation. Pretransplant prophylaxis for a positive purified protein derivative, if given, is with isoniazid 300 mg/d up to, or following, transplantation. Post-transplant treatment is more accepted, but due to the possible high rate of hepatotoxicity, many centers have chosen not to administer prophylaxis. Treatment of pulmonary disease should include at least two to three drugs (depending on resistance patterns in the area) for 6 to 9 months. Treatment of

disseminated disease or extrapulmonary disease should include three or four drugs for 12 to 18 months. When starting treatment with isoniazid and rifampicin, care should be taken to increase the glucocorticoid dose twofold and the cyclosporine by threefold to fivefold. This is because rifampicin (and somewhat isoniazid) induces the metabolism of steroids and cyclosporine and FK506 through the P450 cytochrome system. (*Adapted from Med Lett Drugs Ther* [8]; with permission.)

Protozoal/Parasitic Infections

DIAGNOSTIC TECHNIQUES FOR PNEUMOCYSTIS CARINII INFECTION

Technique	Yield	Complications	Comments*
Routine sputum	Poor	Rare	Cultures needed
Induced sputum	30%–75%	Rare	First choice; excellent in AIDS
Transtracheal aspiration	Fair (with experience)	Common: bleeding; subcutaneous air	Rarely worthwhile
Gallium scan	Nonspecific	Injection site	Positive in >95% of infected patients
Bronchoalveolar lavage (BAL)	>50% (>95% in AIDS)	Bleeding, aspiration fever, bronchospasm	Wedge terminal BAL with immunofluorescence
BAL/brushing	As for BAL alone	As for BAL	Not useful for <i>P. carinii</i>
BAL/transbronchial biopsy	Over 90% (all patients)	See BAL; pneumothorax	Impression smears; cultures/pathology
Open lung biopsy	Over 95% (all patients)	Anesthesia, air leakage, altered respiration, wound infection	"Gold standard" noninfectious/infectious processes; large sample
Needle aspirate	Up to 60%	Pneumothorax, bleeding	Best in localized disease

*All samples should be cultured and stained for bacteria (including mycobacteria), fungi, viruses, and examined for protozoa. Optimal procedures depend on the locally available expertise.

FIGURE 10-29

Diagnostic techniques for *Pneumocystis carinii* infection. (Adapted from Fishman [9]; with permission.)

THE TREATMENT OF PNEUMOCYSTIS CARINII

Agent(s) (route)	Dose	Options [†]
Trimethoprim and sulfamethoxazole (TMP-SMZ) (IV/po)	15 mg/kg/d TMP (to 20) 75 mg/kg/d SMZ (to 100)	Treat through rash: reduce TMP or SMZ by one half; desensitize
Pentamidine isethionate (IV)	4 mg/kg/d 300 mg/d maximum	Lower dose (2–3 mg/kg); IM not advised
Dapsone (po) with TMP (po/IV)	100 mg/d 15–20 mg/kg/d (900 mg)	Methemoglobinemia; G6PD; may be tolerated in sulfadiazine allergy
Clindamycin (IV/po) and primaquine	600–900 mg q 6 h 15–30 mg base po qd	Methemoglobinemia; diarrhea (pyrimethamine for primaquine)
Trimetrexate (IV) with folinic acid (po) (leucovorin)	30–45 mg/m ² /d 80–100 mg/m ² /d	Leukopenia, anemia; thrombocytopenia; relapse common
Pyrimethamine (po)	Load 50 mg bid x 2 d, then 25–50 mg qd	Not studied fully
with sulfadiazine	Load 75 mg/kg, then 100 mg/kg/qd	Maximum 4 g in two doses; up to 8 g
Atovaquone (po)	750 mg po tid	Variable absorbance, improved with fatty food; rash

*Adjunctive therapies (see text): corticosteroids (high dose with rapid taper); possibly interferon gamma; granulocyte-macrophage colony-stimulating factor.

[†]Based on clinical judgment of physicians; some agents are not approved by the Food and Drug Administration for this indication.

FIGURE 10-30

The treatment of *Pneumocystis carinii* infection. (Adapted from Fishman [9]; with permission.)

ANTIBIOTIC THERAPY FOR TOXOPLASMA GONDII INFECTION

Drug [†]	Dose	Duration	Comments
Pyrimethamine	100 mg po x 2 (then) 25 mg–50 mg po, qd, or qod	Load 3–6 wk	Bone marrow suppression; may give folic acid 5 mg po/im qod except leukemia
Sulfonamide	Sulfadiazine 4 g po (then 1–1.5 g po qid or tri-sulfapyridine; (75–100 mg/kg/d)	3–6 wk	Decrease dose for neutropenia; sulfa allergy common
Clindamycin	600–1200 mg IV or 600 mg po q6h	3–6 wk	Slower resolution than with sulfa; <i>C. difficile</i> colitis
Spiramycin	1 g po tid or qid	3–6 wk	In pregnancy or sulfa allergy with pyrimethamine; CNS data limited

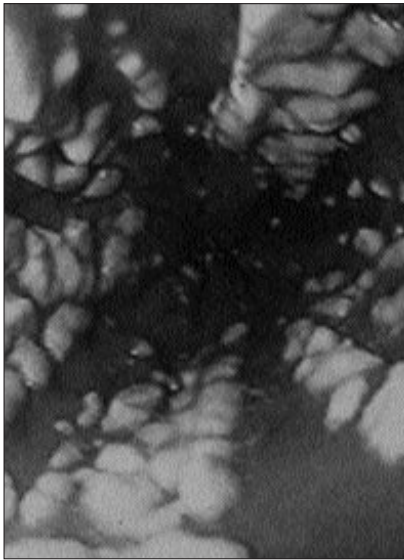
*Active infection: twice weekly blood counts are necessary to detect bone marrow suppression resulting from therapy. Lifelong prophylaxis after acute infection is recommended in transplant and AIDS patients.

[†]Investigational: trimetrexate, atovaquone, macrolides, gamma interferon.

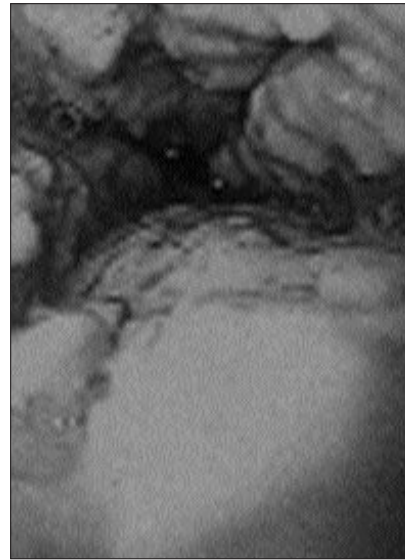
FIGURE 10-31

Antibiotic therapy for *Toxoplasma gondii* infection. (Adapted from Fishman [9]; with permission.)

Yeast and Fungal Infections

FIGURE 10-32
(see Color Plate)

Candida esophagitis
seen on esophago-
gastroduo-
denoscopy.

FIGURE 10-33
(see Color Plate)

Endoscopic view of
severe esophagitis.

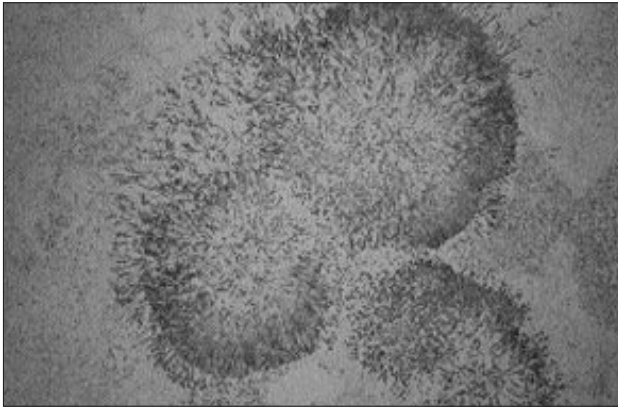


FIGURE 10-34 (see Color Plate)

Displayed are *Aspergillus* as fungus balls, which are proliferating masses of fungal hyphae. The hyphae are septate, 5 to 10 μm thick, and branch at acute 40° angles. *Aspergillus* frequently invades blood vessels, causing hemorrhage and necrotizing inflammation with downstream infarction. This image shows three fungus balls in the lung (Gomori-Ammon stain for fungi).

TREATMENT OF FUNGAL INFECTIONS IN THE SOLID-ORGAN TRANSPLANT RECIPIENT BY CATEGORY OF INFECTION

Category of infection	Prophylactic	Preemptive	Definitive
Mucocutaneous candidiasis	Nystatin (oral)		Fluconazole
Candiduria		Fluconazole*	Amphotericin B bladder irrigation; Fluconazole†
Invasive candidiasis			
Life-threatening			Amphotericin B (0.5–1.0 mg/kg) +/- flucytosine
Catheter-associated‡			Amphotericin B Fluconazole in selected cases§
Less-ill, sensitive organism			Fluconazole
Aspergillosis		Itraconazole¶	Amphotericin B (1.0–1.5 mg/kg)**
Mucormycosis, Phaeohyphomycosis, Hyalohyphomycosis			Amphotericin B (1.0-1.5 mg/kg)**
Cryptococcosis		Fluconazole††	Amphotericin B + flucytosine x 2 wk, then Fluconazole x 4–10 wk if clinical and microbiologic response
Histoplasmosis, Coccidioidomycosis, Blastomycosis	?Itraconazole‡‡	Itraconazole††	Amphotericin B; itraconazole may be useful as primary therapy
<i>Pneumocystis carinii</i>	TMP/SMX		TMP/SMX

*Asymptomatic candiduria in renal transplant recipients

†Not *T. glabrata* or other resistant species

‡Removal of catheter

§Less ill, sensitive organism, nephrotoxicity owing to amphotericin B and proven microbiologic and clinical response

¶Pulmonary colonization immediately before or after transplantation

**Surgical débridement where possible

††Excision of focal pulmonary nodule due to *C. neoformans* or *H. capsulatum*

‡‡For coccidioidomycosis in endemic areas

FIGURE 10-35

Treatment of fungal infections in the solid-organ transplant recipient by category of infection. TMP/SMX—trimethoprim-sulfamethoxazole. (Adapted from Hadley and Karchmer [10]; with permission.)

Hepatitis B

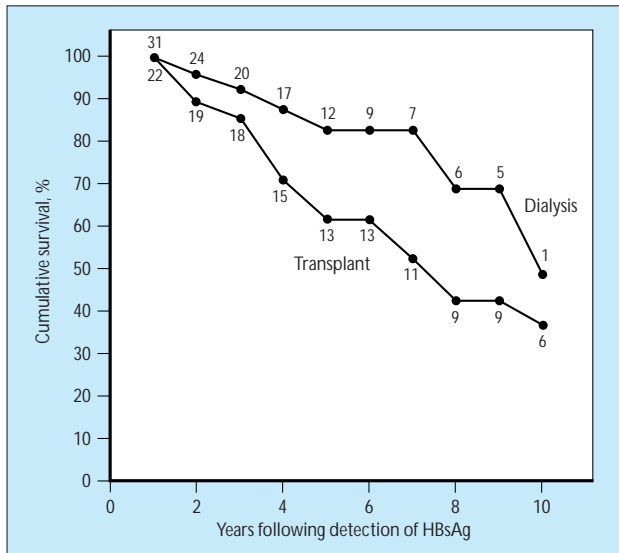


FIGURE 10-36

Survival of hepatitis B virus (HBV)-infected patients with end-stage renal disease treated with either dialysis or transplantation. Patients infected with HBV (hepatitis B surface antigen [HBsAg] positive) on hemodialysis were matched for age with 22 previously transplanted HBsAg-positive patients. This study shows the reason for concern and investigation as to the safety of transplantation in HBV-infected patients. Although there are other studies showing a significantly decreased survival in patients transplanted with HBV infection, most currently show equivalent survival of over 10 years. The cause of death in the HBV-infected group, however, may more often be from infection and liver failure than from cardiac disease.

The safety of transplantation in HBsAg-positive patients has been debated for over 25 years. Increased mortality, if seen, is usually seen beyond 10 years following transplantation and is often secondary to liver failure or sepsis. The acquisition of hepatitis B infections post-transplant, however, does carry a worse prognosis. Virtually all patients with severe chronic active hepatitis, and 50% to 60% of those with mild chronic active hepatitis on liver biopsy prior to transplantation, will progress to cirrhosis. Patients with chronic persistent hepatitis usually do not show histologic progression over 4 to 5 years of follow-up, although mild lesions do not guarantee preservation of hepatic function over longer periods. The complete natural history of hepatitis B following transplantation is not known, as biopsies have been performed largely in those who have abnormal liver function tests; however, one recent study, that included analyses of all individuals who were HBsAg positive around the time of transplantation, has shown histologic progression in 85.3% of those who were rebiopsied with the development of hepatocellular carcinoma in eight of 35 patients who developed cirrhosis. A key to management of patients who were HBsAg positive following transplantation is to periodically monitor the liver by ultrasound and to perform a serum alpha-fetoprotein level to detect hepatocellular carcinoma at the earliest possible stage. The key to minimizing the effects of hepatitis B infections following transplantation, however, is to administer the hepatitis B vaccine as early as possible in the treatment for end-stage renal disease. It is noted that 60% will develop antihepatitis B titers when vaccinated while on dialysis compared with only 40% of those who have already been transplanted. Co-infection with hepatitis C may result in more aggressive liver disease but so far has not led to a marked decrease in patient survival. Because of the high risk of acute renal failure or rejection with the use of interferon post-transplant, treatment of hepatitis B with interferon following renal transplantation is not advised. Lamivudine or other experimental antihepatitis agents may be used pretransplant for patients with hepatitis B infection. (Figure adapted from Harnett and coworkers. [11]; with permission.)

POST-TRANSPLANT SURVIVAL IN HEPATITIS B–INFECTED PATIENTS

Author	Year	Patients evaluated, n		1 y, %		3 y, %		5 y, %		10 y, %	
		HBsAg +	HBsAg –	HBsAg +	HBsAg –	HBsAg +	HBsAg –	HBsAg +	HBsAg –	HBsAg +	HBsAg –
Pirson	1977	61	60	94	95			60	80		
Hillis	1979	16	149	55	90	28	80				
Touraine	1989	140	869	94	93			91	88	87	82
Dhar	1991	51	541	92	98			88	93		
Roy	1994	85	172	100	100			75	75	66	68 (8 y)
Pfaff	1997	781	13,287	88.8	91.8			77.6	80.6	61.6	65.8

+—HBsAg positive; ——HBsAg negative.

Later studies have usually shown comparable patient and graft survival in HBsAg-positive patients compared with HBsAg-negative patients. There may only be a slight 3% to 4% difference overall in long-term graft and patient survival in favor of HBsAg-negative patients.

FIGURE 10-37

Post-transplant survival in hepatitis B–infected patients. Later studies have shown comparable patient and graft survival in hepatitis B surface antigen (HBsAg)–positive patients compared with HBsAg–negative patients. There may only be a slight 3% to 4% difference

overall (in favor of HBsAg–negative patients) in long-term graft and patient survival. (Data from Pirson and coworkers [12], Hillis and coworkers [13], Touraine and coworkers [14], Dhar and coworkers [15], Roy and coworkers [16], and Pfaff and Blanton [17].)

CHRONIC HEPATITIS B INFECTION IN HBsAg-POSITIVE RENAL TRANSPLANT RECIPIENTS: RESULTS OF LIVER BIOPSIES PERFORMED PERITRANSPLANT AND A MEDIAN OF 66 MONTHS LATER

	First Biopsy n = 131	66 months →	Second biopsy n = 101
Histology	%		%
Normal	39%		6%
Chronic persistent	25%		18%
Chronic active	25%		42%
Cirrhosis	0%		28%
Miscellaneous	11%		6%

Histologic deterioration was seen in 85.3% of those rebiopsied with hepatocellular carcinoma seen in 8/35 with cirrhosis. Patients had not been treated with anti-HBV agents. 151 patients were HBsAg positive, median age 46, 35 females, 116 males. Immunosuppression in 124 was prednisone and azathioprine and in 27 cyclosporine, azathioprine, and prednisone. The median follow-up was 125 months (range 1 to 320). Median time of HBsAg positivity was 176 months with 20% acquiring HBV infection post-transplant.

FIGURE 10-38

Chronic hepatitis B infection in hepatitis B surface antigen (HBsAg)–positive renal transplant recipients. Results of liver biopsies performed peritransplant and a median of 66 months later in 131 of 151 HBsAg+ patients. Histologic determination was seen in 85.3% of patients rebiopsied, with hepatocellular carcinoma seen in eight of 35 patients with cirrhosis. Patients had not been treated with anti-hepatitis B virus agents. With a median age of 46, 151 patients were HBsAg positive (35 female, 116 male). Immunosuppression in 124 patients was with prednisone and azathioprine, and in 27 patients was with cyclosporine, azathioprine, and prednisone. (From Fornairon and coworkers [18]; with permission.)

CHRONIC HEPATITIS B INFECTION: CAUSES OF DEATH IN 151 HBSAG-POSITIVE PATIENTS OVER 125 MONTHS

Liver related (n = 15)		Not liver related (n = 26)	
Spontaneous bacterial peritonitis	6	Cancer	6
Hepatocellular carcinoma	4	Sepsis	8
Liver failure	5	Cardiovascular	5
Fibrosing cholestatic hepatitis	2	Stroke	3
		Other	4

Death following transplantation in patients with hepatitis is more frequently caused by sepsis and liver failure than in patients with chronic hepatitis.

FIGURE 10-39

Chronic hepatitis B infection. Causes of death in 151 hepatitis B surface antigen (HBsAg)-positive patients over 125 months. Death following transplantation is more frequently due to sepsis and liver failure in patients with hepatitis than in patients without chronic hepatitis. (From Fornairon and coworkers [18]; with permission.)

Hepatitis B virus screening in renal transplant candidates

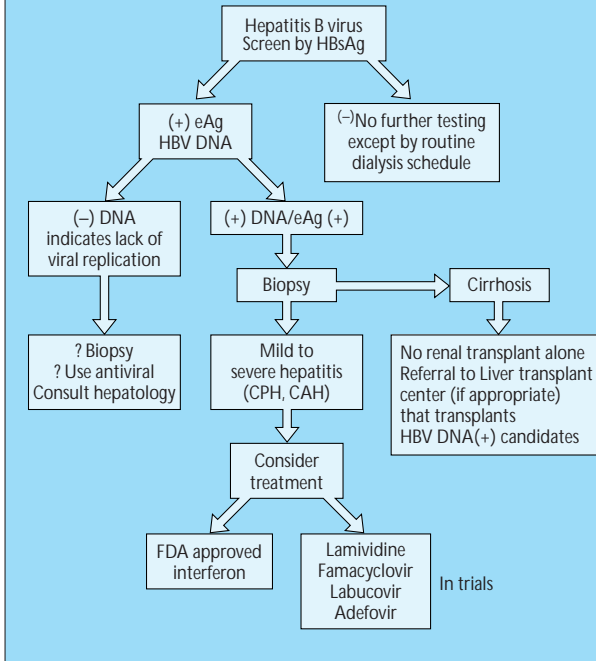


FIGURE 10-40

Hepatitis screening in renal transplant candidates. CAH—chronic active hepatitis; CPH—chronic persistent hepatitis; HBsAg—hepatitis B surface antigen; HBV—hepatitis B virus.

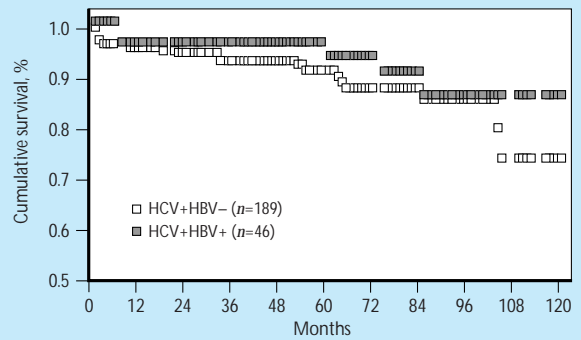


FIGURE 10-41

Patient survival in 235 hepatitis C virus (HCV)-positive patients. Patients coinfectd with HCV and hepatitis B virus (HBV) had comparable survival 12 years after transplant as those infected with HCV alone although fibrosis was more common in dually infected patients. Results were based on 27 biopsies in patients who were both HCV positive and HBV positive and 81 biopsies in patients who were both HCV positive and HBV negative. Over time, liver failure occurred more frequently in patients who were both HCV and HBV positive (17%) than in patients who were both HCV positive and HBV negative (7%). (From Pouteil-Noble and coworkers [19]; with permission.)

Hepatitis C

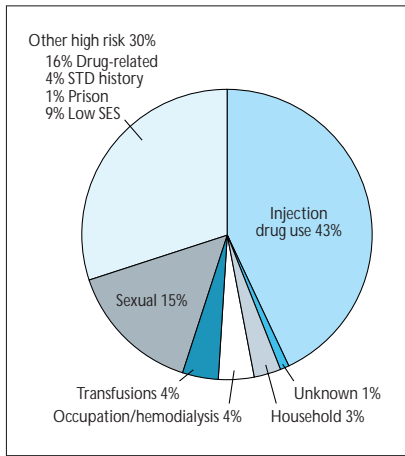


FIGURE 10-42

Risk factors associated with reported cases of acute hepatitis C in the United States (1991 to 1995). Hepatitis C transplant infection prior to transplantation has not been definitively shown in most studies to markedly affect survival for at least 5 years following renal transplantation. Furthermore, hepatitis C–positive individuals who are otherwise good transplant candidates appear to have increased survival when transplanted, compared with staying on dialysis. Liver biopsies performed prior to transplantation have usually shown mild histological changes or chronic persistent hepatitis, but sequential biopsies have not been performed for a long enough period of time and compared with survival to outline the natural history. Transaminase levels do not help to predict histology or outcome. Death in hepatitis C–positive individuals is more often related to infection than in hepatitis C–negative transplant recipients. Post-transplant treatment with interferon alpha has led to an unacceptably high rate of both rejection and acute renal failure secondary to severe interstitial edema without tubulitis. Additionally, except for a few individuals, interferon has not resulted in long-term viral clearance. Most studies show the return of hepatitis C viremia within 1 month following cessation of interferon. At this point it appears that hepatitis G infections (also caused by an RNA virus) in renal transplant recipients, although occasionally associated with slight increases in chronic hepatitis, are not associated with decreased survival.

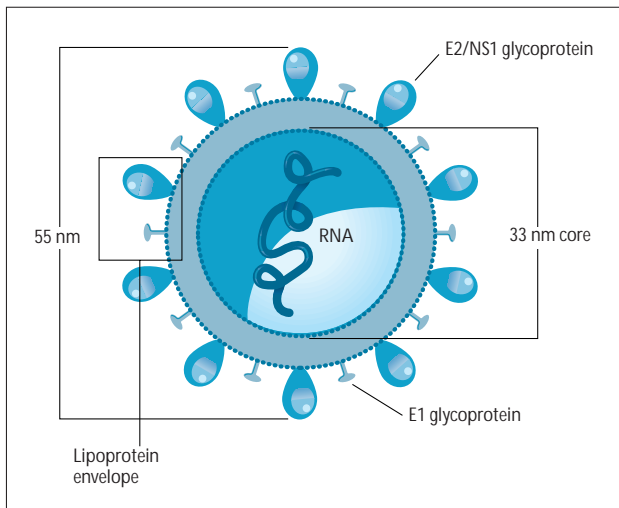


FIGURE 10-43

Proposed structure of the hepatitis C virus.

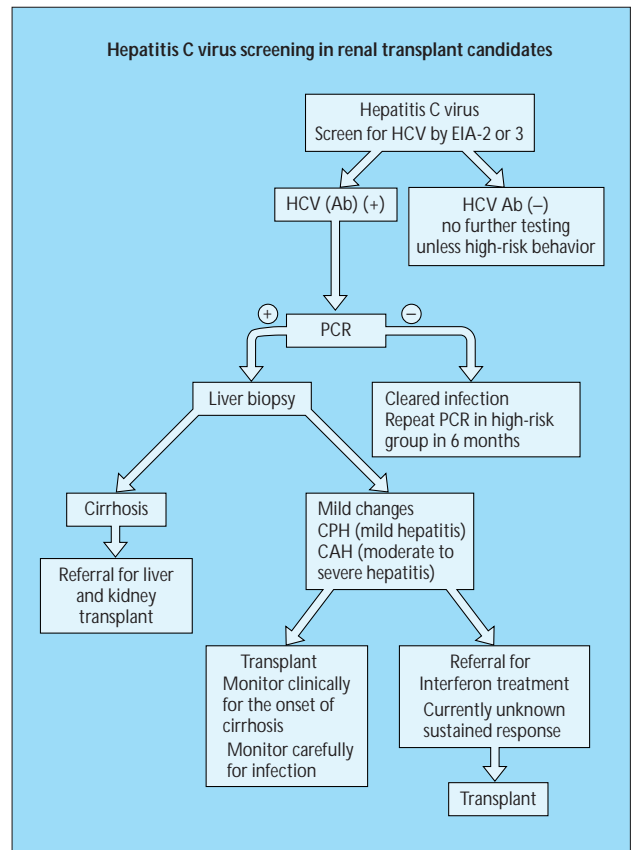


FIGURE 10-44

Hepatitis screening in renal transplant candidates. CAH—chronic active hepatitis; CPH—chronic persistent hepatitis; HCV(ab)—hepatitis C virus antibody; PCR—polymerase chain reaction.

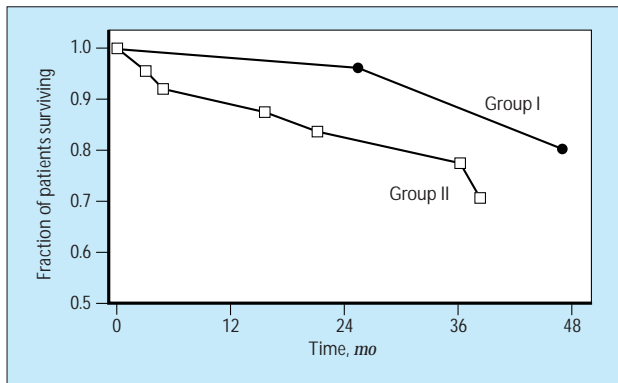


FIGURE 10-45

The survival of hepatitis C virus (HCV)-infected patients after transplant group 1 or while awaiting transplantation group 2. Patients who are transplanted have an increased survival. A small biopsy study of dialysis ($n = 14$) and transplant ($n = 14$) patients showed no difference in histologic progression in transplant recipients. The amount of fibrosis, however, was slightly increased. (Adapted from Knoll and coworkers. [20]; with permission.)

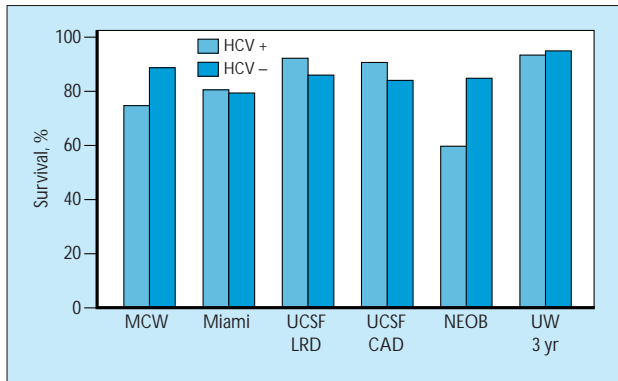
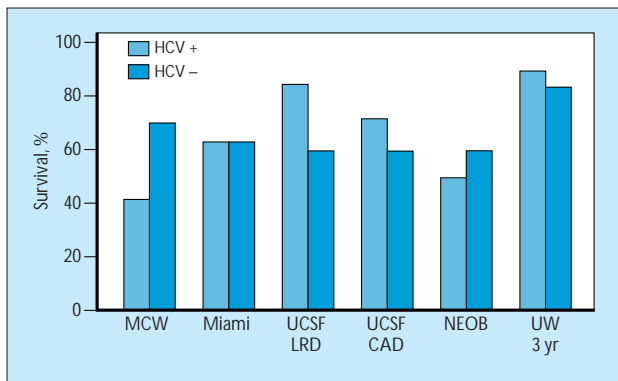


FIGURE 10-46

Five-year patient (*panel A*) and graft (*panel B*) survival in hepatitis C virus (HCV)-positive and HCV-negative patients from recent reports from United States centers. There is no significant difference over 5 years in patient or kidney graft survival. MCW—Medical College of Wisconsin; Miami—University of Miami; NEOB—New England Organ Bank; UCSF CAD—University of California, San Francisco with cadaveric donors; UCSF LRD—University of California, San Francisco, with living related donors; UW—University of Washington.



RENAL AND HEPATIC OUTCOME IN PATIENTS TREATED WITH INTERFERON ALPHA FOLLOWING RENAL TRANSPLANT FOR HCV INFECTION

Author	Thervet	Magnone	Rostaing	Rostaing*	Yasumura
Year	1994	1995	1995	1996	1997
Number treated	13	11	14	16	6
HCV + HBV +	4	1	0	NA	0
Dose mU, SC, TIW	3–5	1.5–5	3	3	6
Normalization of ALT	1	NA	10	NA	6
Discontinued treatment	7	7	7	9	0
Number with cirrhosis	8	NA	1	NA	0
PCR +→PCR –	NA	NA	4	NA	2
Relapse→PCR +	NA	NA	4	NA	0
Acute renal failure	2	0	5	6	0
Rejection	0	7	0	0	1
Lost transplant	0	6	1	3	0
New proteinuria	NA	NA	2	NA	1

*Most are overlapping patients with the 1995 study.

FIGURE 10-47

Renal and hepatic outcome in patients treated with interferon alpha post-renal transplant for hepatitis C virus (HCV) infection. Interferon treatment results in a high rate of transplant acute renal failure or rejection. Transplant biopsies in those with acute renal failure show severe diffuse edema. Acute renal failure is not very responsive to steroids. Virologic clearing is rare, as HCV-RNA is detectable, on average, 1 month after discontinuing interferon if the polymerase chain reaction (PCR) became negative during treatment. ALT—alanine aminotransferase; SC—subcutaneously; TIW—three times a week. (*Data from* Thervet and coworkers [21], Magnone and coworkers [22], Rostaing and coworkers [23,24], and Yasumura and coworkers [25].)

Hepatitis G

HEPATITIS G VIRUS IN RENAL TRANSPLANTATION: PREVALENCE OF INFECTION AND ASSOCIATED FINDINGS

Author	Dussol	Murthy*	Fabrizi
Year	1997	1997	1997
Location	Marseille	NEOB	Milan
% infection	28%	18%	36%
% with HCV infection	12.5%	28%	91%
% with chronic ALT elevation	12.5%	35%	18%
Rejection rate	Unchanged	Unchanged	NA
% with HBsAg	8%	NA	18%
Survival versus HGV negative	NA	Unchanged	NA

*One patient may have acquired HGV through the donor organ. Five of 10 pretransplant positive patients became HGV RNA negative post-transplant.

FIGURE 10-48

Hepatitis G virus (HGV) in renal transplantation: prevalence of infection and associated findings. Hepatitis G virus is an RNA virus of the flaviviridae family. Hepatitis G virus was isolated independently by two different groups of investigators and called hepatitis GB viruses by Simmons and colleagues, and hepatitis G virus by Lenin and colleagues. It now appears that GB virus-A and GB virus-B are tamarin viruses and GBV-C is a human virus with

sequence homology of more than 95% with the hepatitis GV sequence. The virus has been shown to be transmitted by transfusions, including plasma products, by frequent parenteral exposure, including intravenous (IV) drug abuse, by sexual exposure, and by mother to child transmission. In the United States, the prevalence of hepatitis G virus is 1.7% among healthy volunteer blood donors, 8.3% among cadaveric organ donors, and 33% among IV drug abusers. Among chronic hemodialysis patients, the prevalence of hepatitis G virus RNA has been variable, ranging from 3.1% in Japan to 55% in Indonesia and some areas in France. Likewise, the reported incidence of co-infection with hepatitis B virus (HBV) and hepatitis C virus (HCV) is extremely variable.

Hepatitis G virus RNA is detected by reverse transcriptase polymerase chain reaction (PCR). The development of reliable serologic assays for hepatitis G has been difficult due to the lack of linear epitopes expressed by hepatitis G virus. The risk for pretransplant hepatitis G infection is associated with increasing numbers of blood transfusions and with longer duration of dialysis. Post-transplantation, most patients with hepatitis G virus remain viremic; however, patients have been shown to clear the virus post-transplant. At this time, hepatitis G virus does not appear to invoke a poor outcome after transplantation, either in the form of severe liver disease or increased mortality; however, the long-term studies needed to provide a firm conclusion about this have not been performed. The question of transmission of hepatitis G virus via transplantation is still under investigation. NA—not available; NEOB—New England Organ Bank. (*Data from* Dussol and coworkers [26], Murthy and coworkers [27], and Fabrizi and coworkers [28].)

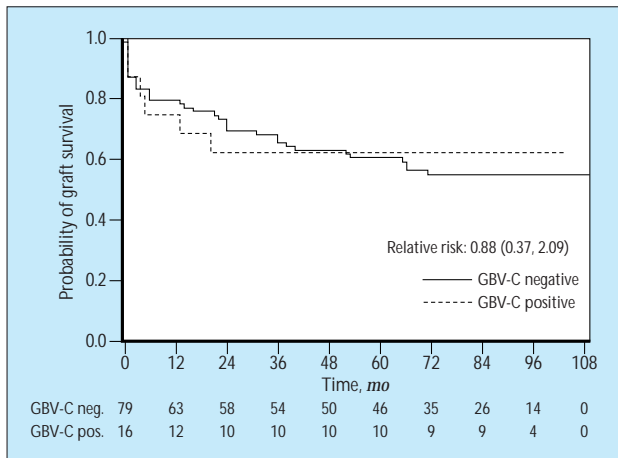


FIGURE 10-49

Kaplan-Meier estimate of graft survival among recipients with GBV-C RNA and without GBV-C RNA before transplantation. Death with a functioning graft is included as a cause of graft loss. The relative risk of graft loss among recipients with pretransplantation GBV-C RNA (and 95% CI of the risk) was calculated using a proportional hazards model. The number of patients at risk at the beginning of each 12-month interval is provided. (Adapted from Murthy and coworkers [27]; with permission.)

Value of Pretransplant Liver Biopsy

HEPATITIS MARKERS AND HISTOPATHOLOGIC DIAGNOSIS FROM LIVER BIOPSIES PRIOR TO TRANSPLANT

	CAH	CPH	CIRH	Normal	HSTAS	Other	Total
HbsAg (+)	2	2	1	1	–	1	7
Anti-HCV (+)	11	4	–	10	2	3	30
HbsAg and anti-HCV (+)	1	–	–	1	–	–	2
Anti-HBs and anti-HCV (+)	8	2	1	9	1	1	22
Anti-HBs (+)	–	–	–	13	–	–	13
Total	22	8	2	34	3	5	74

FIGURE 10-50

Liver biopsy in the evaluation of hemodialysis patients who are renal transplant candidates. Seventy-four patients were biopsied. Forty-six percent of patients had normal or nonspecific changes in their liver biopsies, 30% CAH, 11% CPH, and 3% cirrhosis. Liver enzymes are poor predictors of histology in ESRD. Although with current management HBV-positive and HCV-positive recipients can enjoy comparable 10-year survival to noninfected patients, those with moderate to severe hepatitis more frequently progress histologically and may develop sepsis or liver failure. Liver biopsy aids in the long-term plan for the individual patients' immunosuppression and hepatic and infection monitoring. Furthermore, pretransplant antiviral medications may be beneficial, especially interferon, where post-transplant administration is not advisable because of markedly increased rates of acute renal failure and rejection. (Adapted from Özdoğan and coworkers. [29]; with permission.)

Hepatitis A infections are associated with acute hepatitis and, on occasion, with acute renal failure. Hepatitis A infections can be prevented by either using immunoglobulin injections or, more currently, a hepatitis A vaccine that is given as a two-dose series. This is an inactivated virus that is produced in human fibroblast cell culture and is given to adults as an initial and second dose 6 to 12 months later. The effectiveness of this vaccination has not yet been tested in renal transplant recipients, nor are there specific guidelines on the administration prior to transplantation, but given the lack of toxicity, it may very well be advised in the future to give this to patients with end-stage renal disease and, specifically, to patients who are considering transplantation. CAH—chronic active hepatitis; CPH—chronic persistent hepatitis; CIRH—cirrhosis; HSTAS—hepatic steatosis.

Viral Interstitial Nephritis

VIRAL INTERSTITIAL NEPHRITIS

Adenovirus
BK virus
Cytomegalovirus
Epstein-Barr virus
Herpes simplex virus 1, 2, 6
Varicella-zoster virus
Hantavirus
Hepatitis C virus—possible
HIV

FIGURE 10-51

Viruses that cause interstitial nephritis in renal transplant recipients. Consider this condition when nonspecific inflammation is seen on biopsy or unexplained rejection occurs. Viruses may cause renal disease by direct infection of the glomerular and/or tubular cells or by the immune response directed against virally infected cells. Most commonly nonspecific interstitial inflammation is seen but severe tubular injury by mononuclear cells, peritubular inflammation, and interstitial fibrosis may also be seen. The presentation of virally mediated interstitial nephritis may be acute or subacute. In addition to routine light microscopy, occasionally evaluation by immunofluorescence, electron microscopy, or special stains for light microscopy are necessary to make the diagnosis.

HIV

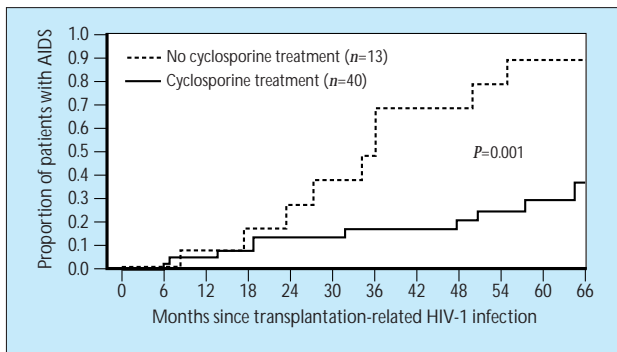


FIGURE 10-52

The occurrence of AIDS in HIV-infected transplant recipients according to immunosuppressive treatment. Immunosuppression included cyclosporine in 40 individuals and no cyclosporine in 13 individuals.

The precise natural history of HIV infection following renal transplantation is still not well delineated. The largest single series from Pittsburgh analyzed 11 patients who were HIV positive prior to transplantation and 14 patients who developed HIV infections following transplantation. Of the 11 patients infected before transplantation, six were alive an average of 3.3 years following transplantation. Five patients had died, however; three of AIDS-related complications. Of the 14 patients infected peritransplantation, seven patients were alive at follow-up an average of 4.8 years later. There had been seven deaths, three due to AIDS. Complications seemed to correlate with increased immunosuppression for rejection.

Another report evaluating 53 patients infected with HIV around the time of transplantation found that patients treated with cyclosporine appeared to have a better long-term prognosis than those who were treated with prednisone and azathioprine.

In summary, although there are no firm conclusions, it appears that there is not much difference between pre- or post-transplant acquisition of HIV infection, although some authors, based on small numbers of patients, have concluded that the age of the patient and the duration of the infection are both prognostic factors. It also appears that approximately 25% of HIV-infected individuals do poorly within the first 6 months of transplantation, especially following antirejection treatment (Rubin, unpublished data). Another 25% of individuals appear to do very well 6 years and beyond following transplantation. The remainder of the individuals seem to develop AIDS within 3 to 3.5 years after transplantation, with an average survival of about 3 months after the onset of AIDS. It has also been noted that cytomegalovirus or other infections that may increase HIV proliferation may influence this outcome, and that prophylactic antimicrobial strategies may alter the "natural history."

Currently, it is advised that all transplant candidates be screened for the presence of HIV antibody and counseled about the possible consequences of further immunosuppression, but not be categorically denied transplantation if they are otherwise asymptomatic. Patient management following transplantation should be focused on the avoidance of large increases in immunosuppression and opportunistic infections, with special attention to the viral, pneumocystic, and mycobacterial infections that these individuals may develop. Antiretroviral strategies in transplantation require study. (*Adapted from Schwarz and coworkers [30]; with permission.*)

Herpes Simplex Virus

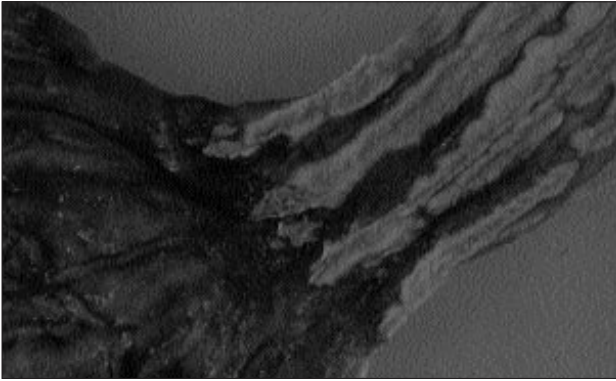


FIGURE 10-53 (see Color Plate)

Linear esophageal ulcers caused by herpes simplex virus (HSV) and *Candida*. Infection with HSV-1 and -2 leads to stomatitis and esophagitis post-transplantation without acyclovir prophylaxis. Additionally, paronychia, corneal ulcers, encephalitis, genital lesions, disseminated involvement of the gastrointestinal tract, pancreas, and liver, and interstitial nephritis has been seen. HSV-6 causes exanthem subitum in children, mononucleosis, and hepatitis. There has been some evidence that reactivation infections may be associated with rejection in transplant recipients. Both reactivation and reinfection may occur. HSV-8 is associated with Kaposi's sarcoma. Prevention of these infections has been achieved using prophylactic acyclovir following transplantation. If clinical symptoms occur from HSV, they usually are treated with acyclovir adjusted for renal function.

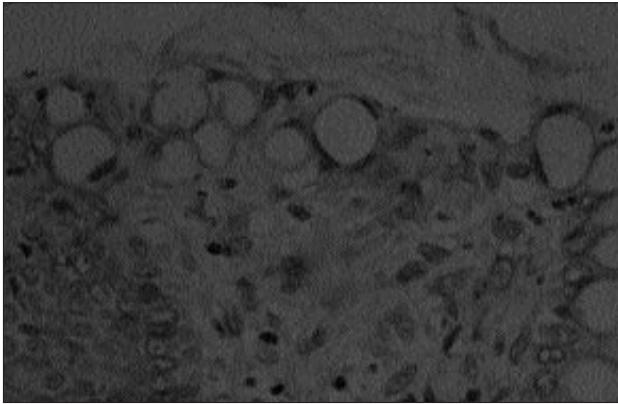


FIGURE 10-54 (see Color Plate)

Varicella-zoster virus (VZV) infection. Primary VZV infections usually result in typical vesicular eruptions of generalized onset without dermatomal localization. Reactivation infection of the virus from the dorsal root ganglion usually causes a dermatomally localized vesicular eruption. By the time of renal transplantation, over

94% of adults have evidence of a prior VZV infection. In those patients previously infected, antibody titers increase following transplantation. Pretransplant screening is recommended to advise the patient on treatment of post-transplant exposures. Post-transplant exposures to zoster or chickenpox in the nonimmune individual should be treated with acyclovir, famcyclovir, or varicella-zoster immune globulin. Immune globulin is rarely required at this time. Patients with the new onset of varicella infection following transplantation or with diffuse zoster should be treated with intravenous acyclovir, 10 mg/kg, three times per day, or famcyclovir depending on renal function. Infection in the transplant recipient, particularly in those who are primarily infected, can result in encephalitis, disseminated intravascular coagulation, pneumonia, bowel involvement, pancreatitis, dermatitis, and hepatitis.

The attack rate in nonimmune individuals of household contacts with varicella infections is 80% to 90%. Therefore, if individuals have not previously had varicella infections at the time of transplant evaluation, vaccination with a live attenuated strain could be considered. Recently this strategy has been used in children prior to renal transplantation. Attack rates in vaccinated individuals may be up to 31%, but the disease that develops is much milder compared with those susceptible individuals not previously vaccinated. Should resistant strains of varicella develop, foscarnet has been effective. Foscarnet is associated with a renal decline in renal function. (Adapted from Friedman-Kien [31]; with permission.)

**FIGURE 10-55**

Adenovirus infection of the colon. Adenovirus infections normally cause asymptomatic infections, coryza, or pharyngitis. Infection in the first decade of life usually protects individuals from future infection as long as the immune system is intact; however, in transplant recipients, adenovirus types 11, 34, and 35 have been shown to cause interstitial pneumonia, conjunctivitis, hemorrhagic cystitis, hepatic necrosis, interstitial nephritis and gastroenteritis, and disseminated disease.

Adenovirus infection may be latent prior to transplant and reactivate post-transplant, or a primary infection may be acquired.

Adenovirus has been shown to infect the bladder, uroepithelial cells, renal tubular cells (distal greater than proximal), the endothelium of the glomeruli and peritubular capillaries, and, occasionally, mesangial cells. The outcome of adenovirus infection is related to the type of immunosuppression and the recipient age. The death rate during active infection in renal transplantation may be as high as 18% but may be even higher in younger patients. The onset of disease after transplantation is usually within 6 months of the transplant.

Clinically, the most frequent symptoms of an adenovirus infection involve difficult micturition, including gross hematuria, fever, and, occasionally, renal dysfunction. The diagnosis is suspected when bacterial cultures are negative but there is gross hematuria. The urinary symptoms usually last 2 to 4 weeks. The diagnosis is made by urine culture or by electron microscopy or light microscopy, where adenoviruses are seen as intranuclear basophilic viral inclusions with a narrow halo between the inclusions and the nuclear membrane. Treatment has been somewhat successful using ganciclovir. Interferon therapy is difficult because of the risk of acute renal failure or rejection in transplant recipients. Furthermore, efficacy is questionable because of the virus' ability to inhibit the mode of action of interferon. Ribavirin has successfully cleared the virus in several immunosuppressed patients. The use of IVIG has not been associated with reliable results. In the future, cidofovir may also be used for the treatment of adenovirus infections, but renal insufficiency and proteinuria may limit use.

CENTRAL NERVOUS SYSTEM INFECTION IN THE TRANSPLANT RECIPIENT

Incidence 5%; mortality up to 85% for CNS infections

Acute to subacute
L. monocytogenes

Subacute to chronic
Cryptococcus neoformans
Mycobacterium tuberculosis
Coccidioides immitis

Focal brain infection
Aspergillus
L. monocytogenes
T. gondii
N. asteroides
Candida albicans
Cryptococcus

Progressive dementia
Polyomavirus, HSV, CMV, HIV

Symptoms

Headache—may be mild, may have little meningismus
Fever—may be mild
± altered consciousness
Cerebrospinal fluid
Lymphocytic pleocytosis
(viral/fungal/MTB)
Hypoglycorrhia
Neutrophilic pleocytosis (bacterial)

Over three-fourths of central nervous system infection is accounted for by

L. monocytogenes
C. neoformans
A. fumigatus

Timing

Early
Listeria
Nocardia
Toxoplasma
Aspergillus

Late—as above and due to chronic enhanced immunosuppression plus *Cryptococcus* and tuberculosis

Diagnosis

Physical examination
CT scan identifies hypodense ring-enhancing lesions
CSF examination
Directed lesional aspirates

FIGURE 10-56

Central nervous system infection in the transplant recipient. CNS—central nervous system; CSF—cerebrospinal fluid; MTB—mycobacterium tuberculosis.

CAUSES OF HEADACHE IN THE TRANSPLANT RECIPIENT

Medications

OKT3 (aseptic meningitis)
 ATG
 IVIgG
 Cyclosporine
 Tacrolimus
 Antihypertensives
 Calcium channel blockers
 ACE inhibitors
 Nitrates
 Hydralazine
 Minoxidil
 Hypertension
 Neck "tension," muscle pulls, ligament irritation
 Sinusitis
 Ocular abnormalities
 Excessive vomiting
 Migraine headaches exacerbated by cyclosporine, tacrolimus, and calcium channel blockers
 Stroke
 Infection of the central nervous system

FIGURE 10-57

Causes of headache in the transplant recipient. ACE—angiotensin-converting enzyme; CNS—central nervous system; ATG—antithymocyte globulin.

WORK-UP OF AN UNEXPLAINED HEADACHE

History

Character, pattern, positional relationships
 Fever, duration of headache and fever
 Location of headache
 Visual, movement, sensory impairment
 Bowel or bladder incontinence
 Trauma
 Medications old and new
 Time of medications and relationships to headache

Physical examination

Eye
 Neurological
 Complete the rest of the examination

If no papilledema or focal neurological deficit→lumbar puncture

If papilledema or focal deficit→CT first if no mass lesion→lumbar puncture

Cerebrospinal fluid is sent for

Cell count and differential
 Protein
 Glucose
 Gram's stain
 Fungal stains
 Acid fast stain
 Fungal culture
 Mycobacterial cultures
 Bacterial cultures
 Cryptococcal antigen
 Save cerebrospinal fluid in addition for other tests including
Histoplasma capsulatum or *Coccidioides immitis* antibody titers

FIGURE 10-58

Work-up of an unexplained headache.



FIGURE 10-59

Epstein-Barr virus (EBV). EBV is associated with asymptomatic infection, mononucleosis, hepatitis, and, rarely, interstitial nephritis. In transplant recipients, posttransplant lymphoproliferative disorder (PTLD) is also associated with EBV. EBV promotes B-cell proliferation, if left unchecked by immunosuppressive agents targeting the T-cell system. This chest radiograph shows multiple pulmonary nodules of PTLD. Symptoms vary from no symptoms to diffuse organ involvement causing dysfunction. Any area of the body may be involved, with frequent sites being the gums, chest, abdomen, and central nervous system.

PTLD occurs during the first posttransplant year in approximately 50% of those developing PTLD. It is seen in 1% to 2% of renal transplant recipients. Primary EBV infection following transplantation and antilymphocyte agent use is associated with an increased risk. Increasing quantitative blood EBV DNA levels may predict the onset of PTLD.

Viral Meningitis

VIRAL MENINGITIS

Causal agents	Coronavirus
Enterovirus	HIV
Coxsackie*	Influenza A, B
ECHO*	Lymphocytic choriomeningitis virus
Poliovirus	Parainfluenza virus
Adenovirus	Rabies virus
Mumps	Rhinoviruses
Arbovirus	Rotavirus
Herpes group†	Japanese encephalitis virus*
Cytomegalovirus*	Tick borne encephalitis virus
Herpes simplex virus 1 and 2*	PML (JC) virus (in development)*
HHV-6*	BK virus (in development)*
HHV-8*	
Varicella-zoster virus*	
Epstein-Barr virus*	

* Cerebrospinal fluid polymerase chain reaction available to make the diagnosis but locations vary

† Increased in transplant patients

FIGURE 10-60

Viruses causing meningitis in transplant recipients. The presentation is usually with fever and headache alone or in conjunction with headache may be the initial symptom. Nuchal rigidity is rare in the transplant patient. Cerebrospinal fluid samples should be saved for viral analysis and analysis should be requested if the diagnosis is not rapidly available from standard studies.

Black Hairy Tongue

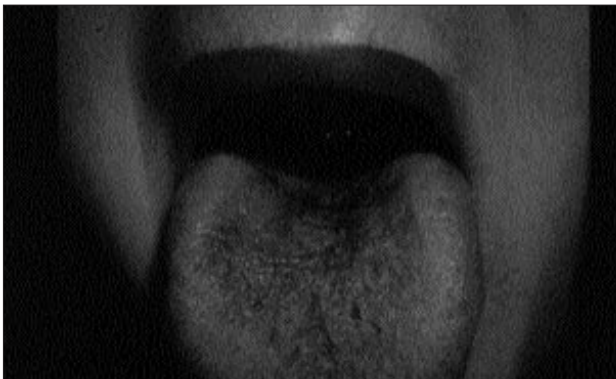


FIGURE 10-61 (see Color Plate)

Black hairy tongue is the result of hypertrophy of filiform papillae of the tongue, often seen in transplant patients after antibiotic treatment. The origin is unknown but is associated with topical or systemic antibiotics, poor oral hygiene, smoking, alcohol, and the use of mouthwashes. Most often there are no symptoms; however, nausea, gagging, taste alteration, or halitosis are reported by some patients. Treatment includes brushing with a soft brush and, occasionally, topical vitamin B, salicylic acid, gentian violet, or surgical removal. This entity is not to be confused with hairy leukoplakia, which is composed of white corrugated plaques on the lateral surface of the tongue. These lesions may be small and flat or extensive and hairy. Microscopic evaluation shows epithelial cells with herpetic viral inclusions, specifically Epstein-Barr virus. Treatment is oral acyclovir.

Tinea Versicolor



FIGURE 10-62 (see Color Plate)

Tinea versicolor (pityriasis versicolor) is a chronic superficial fungal disease caused by *Malassezia furfur*, a yeast normally found on the skin. It is in yeast form in the unaffected skin areas and in the mycelial phase on affected skin. The disease usually is located on the upper trunk, neck, or upper arms. Symptoms may include scaling, erythema, and pruritis. It may appear as slightly scaly brown macules or whitish macules. Treatment options include oral or topical terbinafine (1% cream or gel), oral or topical ketoconazole, oral fluconazole, or topical treatments, such as ciclopiroxolamine, piroctoneolamine, zinc pyrithione, or sulfur-containing substances, such as selenium sulfide; the most common treatment is selenium. Patients are asked to wet themselves in the shower, turn off the water, apply the selenium and let it sit for 10 minutes, and then rinse. Also, oral fluconazole, 200 mg, once or repeated once a week later is a simple and effective treatment. Of note, oral terbinafine, 250 mg, daily for 12 weeks is associated with slightly decreased cyclosporine levels. Terbinafine is an allylamine that binds to a small subfraction of hepatic cytochrome P450 in a type I fashion. Side effects seen during terbinafine use include gastrointestinal distress in up to 5% of patients and skin rashes in 2% of patients.

Kaposi's Sarcoma



FIGURE 10-63 (see Color Plate)

Kaposi's sarcoma of the lower leg in a male transplant recipient. Kaposi's sarcoma is a tumor, perhaps of lymphatic endothelial origin, that presents as purple papules or plaques that advance to nodules of the extremities, oral mucosa, or viscera. In transplant recipients it presents on average by 21 months post-transplant, with the largest number (46%) within the first post-transplant year. It is seen most often in men (3:1) and in those of Arabic, black, Italian, Jewish, and Greek ancestry. It accounts for 5.7% of the malignancies reported to the Cincinnati Transplant Tumor Registry (nonmelanoma skin cancers and in situ carcinomas of the uterine cervix excluded). Transplant programs in Italy and Saudi Arabia have reported higher rates of post-transplant Kaposi's sarcoma. Visceral involvement is less common in the transplant recipient than in the AIDS patient, but it must be remembered that it may be seen in the liver, lungs, gastrointestinal tract, and nodes. Mortality is increased with visceral involvement (57% versus 23%). HHV-8 has been proposed as the causal agent of this tumor; however, not all investigators feel the evidence is conclusive. Of note, the occurrence in AIDS patients is decreased in those who receive foscarnet, cidofovir, and ganciclovir, but not acyclovir. Treatment includes decreasing immunosuppression, local radiation, excision, interferon, or chemotherapy.

Mucormycosis

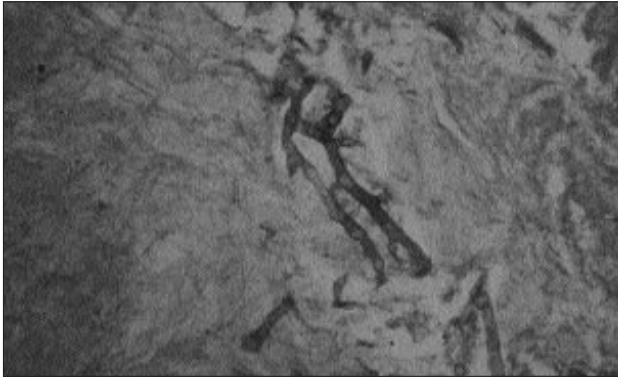


FIGURE 10-64

Mucormycosis is caused by fungi of the order Mucorales, including *Rhizopus*, *Absidia*, and *Mucor*. Mucorales are ubiquitous saprophytes found in the soil and on decaying organic material, including bread and fruit. Human infection is believed to be caused by the inhalation of spores that initially land on the oral and nasal mucosa. Direct inoculation into tissues, however, has been reported.

Most of the spores, once in the tissue, are contained by the phagocytic response. If this fails, as it often does in patients with diabetes mellitus and those otherwise immunosuppressed, germination begins and hyphae develop. The hyphae, as shown in the micrograph, are large, nonseptate, rectangular, and branch at right angles. Infection begins with the invasion of blood vessels, which causes necrosis and dissemination of the infection. The most common site of involvement is the rhino-orbital-cerebral area, accounting for approximately 70% of cases; however, pulmonary, cutaneous, gastrointestinal, and disseminated infection may be seen. The chest radiograph during pulmonary infections may show an infiltrate, nodule, cavitory lesion, or pleural effusion. Gastric involvement may range from colonization of peptic ulcers to infiltrative disease with vascular invasion causing perforation. Although classic for mucormycosis, a black eschar of the skin, nasal mucosa, or palate is present in only about 20% of patients early in the course of the disease and cannot be relied on for assistance in early diagnosis. Survival is dependent on early diagnosis. Diagnosis is by biopsy with classic histologic findings and by culture of tissue. Treatment includes amphotericin B, surgical removal of the lesion, packing of the sinus areas with amphotericin B-soaked packs, and perhaps hyperbaric oxygen. Liposomal amphotericin B has also been effective. Treatment must include both surgery and amphotericin B.

Condyloma Acuminata



FIGURE 10-65

Condyloma acuminata (anogenital/venereal warts) are caused by infection with human papillomavirus 6 or 11. In transplant recipients they may become extremely extensive. Treatment has included fluorouracil, podophyllin, podophyllotoxin, intralesional interferon, topical interferon, systemic interferon, and, more recently, imiquimod, which causes the induction of cytokines, especially

interferon alpha. Lesions have responded in 50% of nontransplant patients receiving the 5% cream. Invasive treatments have included surgical excision, cryotherapy, electrocautery, and carbon dioxide laser. Recurrences are common. **A**, Condyloma acuminata in a male transplant recipient. **B**, Condyloma acuminata in a female transplant recipient.

Verruca Vulgaris

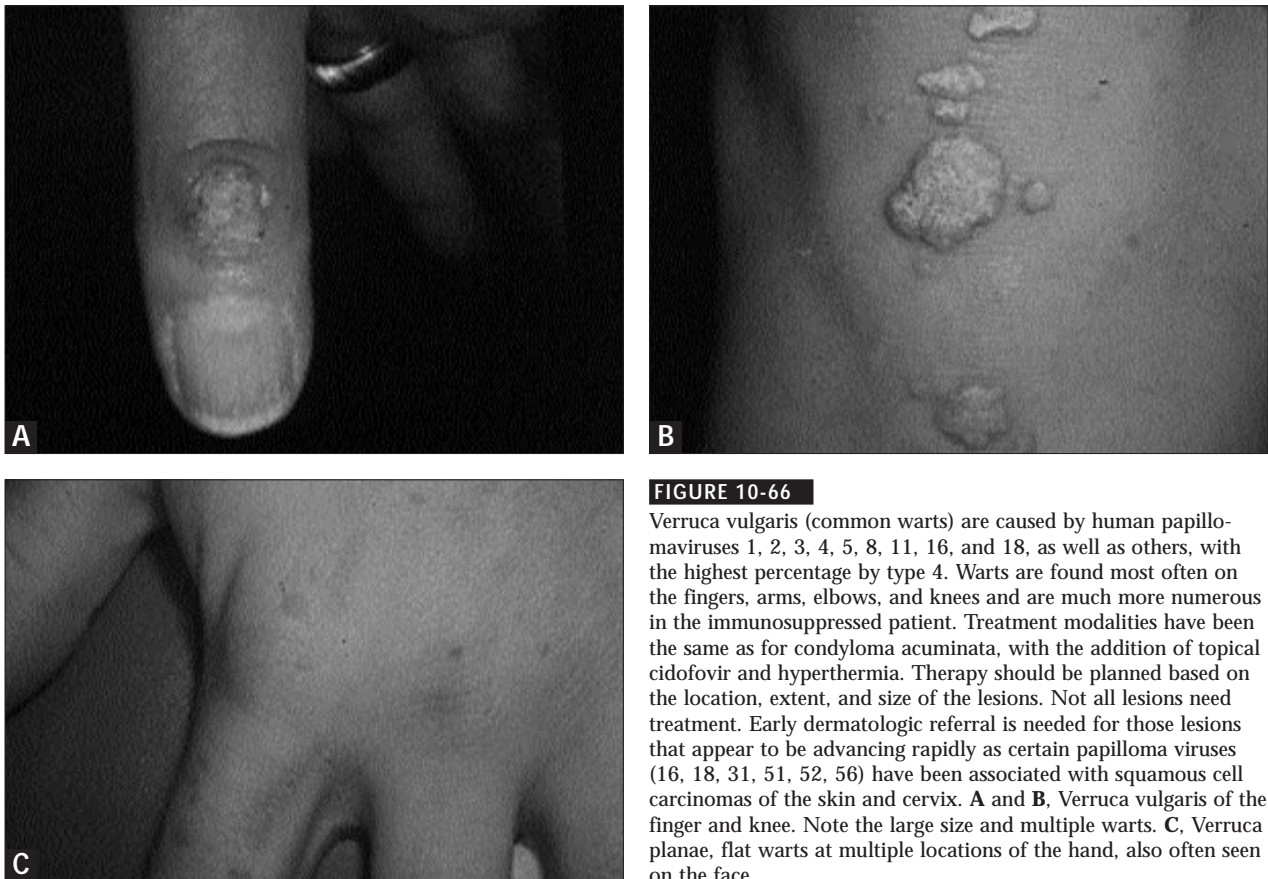


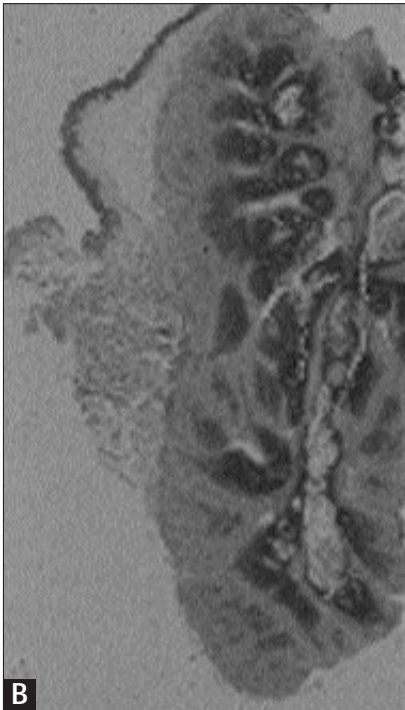
FIGURE 10-66

Verruca vulgaris (common warts) are caused by human papillomaviruses 1, 2, 3, 4, 5, 8, 11, 16, and 18, as well as others, with the highest percentage by type 4. Warts are found most often on the fingers, arms, elbows, and knees and are much more numerous in the immunosuppressed patient. Treatment modalities have been the same as for condyloma acuminata, with the addition of topical cidofovir and hyperthermia. Therapy should be planned based on the location, extent, and size of the lesions. Not all lesions need treatment. Early dermatologic referral is needed for those lesions that appear to be advancing rapidly as certain papilloma viruses (16, 18, 31, 51, 52, 56) have been associated with squamous cell carcinomas of the skin and cervix. **A** and **B**, Verruca vulgaris of the finger and knee. Note the large size and multiple warts. **C**, Verruca planae, flat warts at multiple locations of the hand, also often seen on the face.

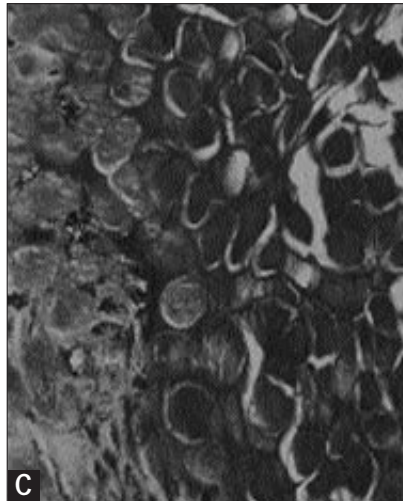
Molluscum Contagiosum



A



B



C

FIGURE 10-67

Molluscum contagiosum is an infection of the skin caused by the molluscum contagiosum virus, a member of the pox virus family. Molluscum does not grow in culture or infected laboratory animals. Manifestations are pearly, pink, dome-shaped, glistening, firm lesions; in immunosuppressed patients, however, they may be over 1 cm in diameter and multiple lesions may occur together. The infection usually lasts up to 2 months in immunocompetent patients, but a chronic, recalcitrant, and disfiguring infection may occur in immunosuppressed patients. The virus is contracted and spreads via close contact with an infected person, fomites, or via autoinoculation. The incubation period is 2 weeks to 6 months. The diagnosis is made visually or by direct examination of curettings from the center of the lesion showing molluscum intracytoplasmic inclusion bodies. Treatment is started for the prevention of spreading, to relieve symptoms, and for cosmetic reasons. Treatment includes cryotherapy, curettage, podophyllin, cantharidin, trichloroacetic acid, phenol, salicylic acid, strong iodine solutions, lactic acid, tretinoin, silver nitrate, and interferon alpha topical or intralesional, and possibly oral cimetidine, with adhesive tape occlusion. None of the available treatments result in a rapid or definite clearance in the immunosuppressed patient. Treatment of the underlying retrovirus infection has been shown to help in AIDS patients, and perhaps reviewing the degree of immunosuppression in the transplant patient will help. **A**, Molluscum contagiosum papule. Note pearly umbilicated appearance. **B**, Histologic slide of molluscum showing a cross section of the papule. **C**, Close-up view of the molluscum bodies.

Intestinal Protozoa

SIMILARITIES AMONG THE INTESTINAL SPORE-FORMING PROTOZOA

History

Identified as human pathogens in recent decades
Once considered rare pathogens; now known to commonly cause infections
The AIDS epidemic increased awareness and recognition

Biology

Protozoa
Intracellular location in epithelial cells of the intestine
Spore or oocyst form is shed in stool

Pathogenesis of diarrhea

Unknown; possible abnormalities of absorption, secretion, and motility
Intense infection of small bowel associated with dense inflammatory infiltrate
May be associated with villus blunting and crypt hyperplasia
Nonulcerative and noninvasive*
Gut function and morphology related to number of organisms†

Epidemiology

Common in tropical regions and places with poor sanitation
Transmission is through fecal-oral route, person-to-person contact, and water or food‡
Endemic disease of children‡
Common source of epidemics in institutions and communities‡
May cause traveler's diarrhea

Clinical manifestations

Asymptomatic infection
Self-limited diarrhea, nausea, and abdominal discomfort in healthy children and adults
Prolonged (subacute) diarrhea in some immunocompetent patients‡
Chronic diarrhea in immunodeficient patients

Diagnosis

Microscopic stool examination should be initial approach
Detection of cysts or spores in stool requires expertise and proper stains

Antibiotic treatment

Not usually indicated in healthy persons with acute infection
Indicated for chronic infection in immunodeficient patients‡

*Septata intestinalis may invade the mucosa.

†Probably true for all; conclusively shown only for cryptosporidia.

‡Not proven for microsporidia.

FIGURE 10-68

Cryptosporidia, *Isoospora*, cyclospora, and microsporidia are intestinal spore-forming protozoa that infect enterocytes predominantly of the small intestine. Infection occurs by ingesting the spores (oocysts) by person-to-person contact or ingesting contaminated food or water, including city or swimming pool water [32]. Infections in immunocompetent individuals may be asymptomatic or self-limited and associated with mild to moderate diarrhea and, less frequently, nausea, abdominal cramping, vomiting, and fever.

In immunodeficient patients, especially those with T-cell impairment, the infections may cause severe persistent diarrhea. The most common infection among the intestinal protozoas is cryptosporidium. The general prevalence of cryptosporidia in stool specimens in Europe and North America is 1% to 3%, and in Asia and Africa is 5% to 10%. Antibodies to cryptosporidia, however, have been found in 32% to 58% of adults. (*Adapted from Goodgame [33]; with permission.*)

Histoplasmosis

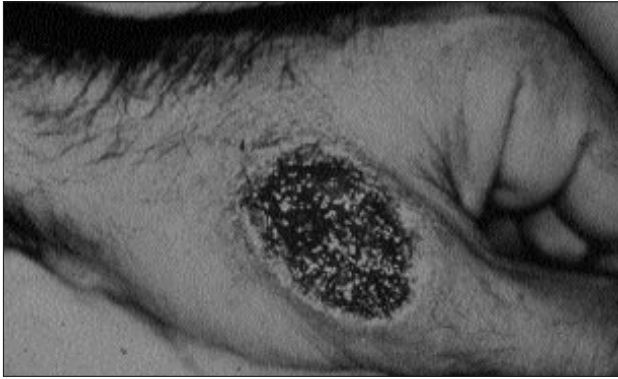


FIGURE 10-69

Histoplasmosis is caused by the thermal dimorphic fungus *Histoplasma capsulatum* that exists in its mycelial phase in nature and in the yeast form in the human body. It is found in the soil enriched with bird or bat droppings in the Ohio and Mississippi River Valleys and in Texas, Virginia, Delaware, and Maryland. Disease is caused by primary infection or by reactivation of latent infection. Primary infection is acquired by inhalation of infectious microconidia, by direct inoculation into the skin, or via an infected allograft. Once the microconidia is lodged in the alveolar and

interstitial spaces, it becomes a yeast, multiplies intracellularly, and disseminates until cell-mediated immunity develops (2 to 10 weeks). Organisms that disseminate concentrate in the reticuloendothelial system. Disseminated disease is marked by fever, weight loss, weakness, fatigue, and mild respiratory symptoms. There may also be organ-specific symptoms, including those of urinary tract obstruction. *Histoplasma* may be found in the glomerular capillary macrophages or macrophages within the interstitium and be associated with focal medullary necrosis or papillary necrosis. The most common symptom of infection is fever, and often there are skin lesions, as shown in this figure, but central nervous system involvement is rare in transplant patients, as are abnormal chest radiographs. When present, chest radiographic findings include diffuse, nodular, patchy, or miliary infiltrates; hilar adenopathy is uncommon. Diagnosis is made by identification of the yeast on a smear, histopathologic detection of intracellular organisms in viable pulmonary tissue, a fourfold rise in antibody titers (only seen in about 50% of immunosuppressed patients), culture of the blood or tissue, or a urine antigen assay. Identification of the organism causing culture growth of a white, fuzzy mold (*Histoplasma*, *Blastomyces*, *Coccidioides*) is now performed by DNA hybridization. The bone marrow may be the most reliable source for sampling and staining for organisms. Treatment is amphotericin B occasionally, with long-term oral itraconazole after completing amphotericin. Resolution of infection may be monitored by following the *Histoplasma* urinary antigen.

Cryptococcosis

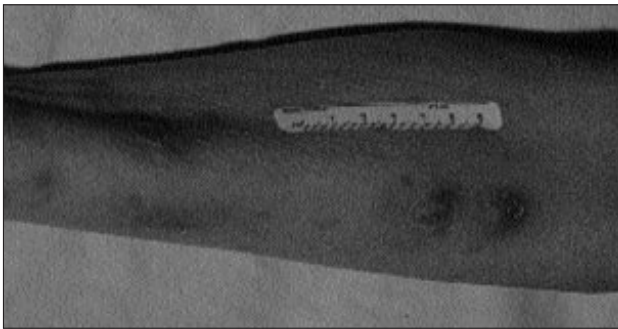


FIGURE 10-70

Cutaneous cryptococcosis, multiple lesions on the arm. *Cryptococcus neoformans* is an encapsulated yeast that exists worldwide, predominantly in the soil contaminated by bird and other animal droppings. Infection is through inhalation with dissemination to the central nervous system (CNS), skin, mucous membranes, bone, bone marrow, and genitourinary tract. Infection has also occurred through the renal allograft. The most common disease site is the

CNS, where patients present with headache, fever, mental confusion, seizures, papilledema, long tract signs, or, uncommonly, meningismus. The onset of infection is anywhere from 6 months to years following transplantation. The onset may be very insidious, with nausea and headache occurring for weeks to months before the fever develops. Pulmonary involvement presents asymptotically or with dyspnea and cough. The chest radiograph shows wide variability in that circumscribed pulmonary nodules, alveolar infiltrates, interstitial infiltrates with or without effusions, and cavitation may be seen. Cutaneous disease may be the first sign of dissemination in up to 30% of cases. Diagnosis is made by the identification of the yeast in the cerebrospinal fluid (CSF) or pulmonary secretions, the detection of cryptococcal antigen in the CSF or blood, or culture. Amphotericin B is the most common agent used for treatment, with some also favoring the use of flucytosine and perhaps azole therapy for maintenance to prevent relapse. Specific patients may be treated with fluconazole alone. Serial determinations of the serum cryptococcal antigen, which is positive in over 95% of patients with cryptococcal meningitis, may help to follow and modify the course of therapy. Patients should be treated until the cryptococcal antigen is negative, and then for another 2 to 4 weeks for added safety.

Herpes Simplex



FIGURE 10-71 (see Color Plate)

Primary oral herpes simplex, mucosal membrane showing vesicles and ulceration.



FIGURE 10-72 (see Color Plate)

Primary herpes simplex stomatitis.



FIGURE 10-73

Cutaneous herpes simplex-herpetic whitlow. This condition may be confused with a bacterial infection.

Central Nervous System Infections

CEREBROSPINAL FLUID FINDINGS BY TYPE OF MENINGITIS

Type	WBC Count (per mm)	Differential, %	Protein Level, mg/dL	Glucose level, mg/dL	Stain used
Viral	5–500	>50 lymphocytes	30–150	Normal to low	Gram's
Fungal	40–400	>50 lymphocytes	40–150	Normal	India ink and cryptococcal antigen
Tuberculous	100–1000	>80 lymphocytes	40–150 (may exceed 400)	Normal to low	Acid-fast
Bacterial	400–100,000	>90 PMNs	80–500	<35	Gram's

FIGURE 10-74

Cerebrospinal fluid findings in patients with bacterial meningitis. (Adapted from Maxon and Jacobs [34]; with permission.)

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