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Introduction

SOT recipients are at high risk for infections due to the complexity of surgical procedures combined with the impact of immunosuppression. The sources of infections basically originate from the recipient prior to or during transplant, the donor organ, and environment exposures [1]. In general, the major types of infection are predicted by the timing of infections after transplant [1].

First Month After Transplant

Three factors are important in determining the risk of infections during this period. First, as after any surgical procedures, *surgical site infections* (SSIs) are the most important. This in turn is influenced by the organs being transplanted, the surgical techniques and technical difficulties. A good understanding of the surgical aspects of transplantation and

their complications is very important in caring for recipients after transplantation. Along these lines, specific organ transplant predispose patients to unique spectrums of infection: urinary tract among renal transplant recipients, intra-abdominal infection among liver, small bowel, or multivisceral transplant recipients, and pneumonia among lung transplant recipients. Second, *nosocomial infections* such as hospital-acquired or ventilator-associated pneumonia, catheter-related blood stream infections, antibiotic-associated diarrhea, and catheter-related urinary tract infections are also important and related to the duration of hospitalization. Lastly, *donor-derived infections* from bacteria, viruses (i.e. West Nile Virus, Lymphocytic Choriomeningitis Virus, Rabies, Human Immunodeficiency Virus, etc.) or parasites (*Trypasonoma cruzi*) and *recipient-derived infections* can also contribute to these early onset infections. At this stage, the net state of immunosuppression has not been prolonged enough to predispose to opportunistic infections. The only virus that might cause significant morbidity and mortality early after transplant is *Herpes simplex virus* (HSV), which usually reactivates in the recipient; the routine use of acyclovir or anti-cytomegalovirus (CMV) prophylaxis has significantly reduced its incidence.

Between the Second and Sixth Months After Transplant

This is the peaked time for opportunistic infections due to: *CMV*, *Aspergillus*, *Pneumocystis*, *Toxoplasma*, *Nocardia*, and *Listeria*. Chronic or latent infections preexisted before transplant such as tuberculosis, endemic fungi due to *Histoplasma*, *Coccidioides*, and *Blastomycosis*, or viral infections due to HBV and HCV might reactivate during this period. Lastly, late manifestations of donor-derived infections (*Strongyloides*, *Toxoplasma gondii*, *Leishmania*, *T. cruzi*) might also occur.

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From 6 Months After Transplantation and Beyond

Most transplant recipients return to full-life in the community. They experience typical infections that non-transplant patients get, including respiratory virus infection, community-acquired bacterial infection, or endemic fungal infections. The clinical manifestations might be more severe than experienced by non-transplant patients. Furthermore, the patients remain at risk for opportunistic infections due to *Nocardia*, *Listeria*, *pathogenic moulds*, *Cryptococcus neoformans*, and *endemic fungi*. Patients who receive anti-CMV prophylaxis might manifest late onset CMV infection during this stage. Reactivation of *Varicella Zoster Virus* might cause devastating disease during this stage.

At any of these stages, if the patients develop acute rejection requiring immunosuppression, the above timetable might be altered, and the clock of infectious complications is reset.

In this chapter, we will focus on organ transplant-related infections during the early period after transplant, and discuss means to prevent them.

Surgical-Related Infections

The most common infections encountered within 30–90 days after transplant are surgically related, and their rates depend on the types of organ transplanted. For the past decade, advances in surgical techniques, knowledge and refinement of immunosuppression strategy, and the use of antibiotic prophylaxis have significantly reduced SSI rate, and the most SSIs are now superficial rather than deep. Despite this improvement, SSIs remain a problem within 90 days of transplant, and when occur, are associated with prolonged hospitalization stay and cost, as well as graft loss. SSIs are classified as superficial (limited to skin and subcutaneous tissue), deep (affecting fascial, or muscular layers) and organ or organ space that is manipulated during transplant procedure [<http://www.cdc.gov/HAI/ssi/ssi.html>. Accessed December 19, 2011]. Cellulitis also occurs, and diagnosed by erythema, tenderness, swelling, and warmth of skin surrounding the wound. The general risk factors for SSIs are those observed with nontransplant general surgery, which include recipient's age, nutritional status, underlying diseases, diabetes mellitus, obesity, and site/complexity of the procedure. The risk of SSI also directly correlates with the dose and virulence of the affected pathogen; certain organ transplant, such as intestinal or lungs, involve a higher burden of microbial colonization or contamination than others [2]. Lastly, each type of organ transplantation is associated with a set of technical and medical problems which predispose to a unique set of infectious complications. These organ-specific infections are discussed below.

Kidney Transplantation

SSIs

Kidney transplant is considered a clean-contaminated procedure since it involves bladder opening which might cause urine spillage into the operative field [3]. The SSI rate is now ~5 %, a rate consistent with the nontransplant urologic procedures [3]. Older donor age, and surgical transplant complications such as vein or artery thrombosis/stenosis, perigraft hematoma, urinomas, urinary leaks, and lymphoceles might predispose to SSIs. Fortunately, most SSIs are superficial and mainly related to contamination from the skin organisms or from urine spillage during bladder opening and anastomosis. Opening the wound and enabling it to heal by secondary intention are usually adequate as treatment of superficial SSIs, but antibacterial agents should be considered in the presence of cellulitis and/or systemic symptoms [3]. Deep infections are generally related to complications such as urinary leaks, and generally require drainage and antimicrobial agents; surgical repair might also be required.

Most SSIs are caused by bacteria, with aerobic Gram positive cocci (*Staphylococcus aureus*, *S. epidermidis*, *Enterococcus* spp.) and Gram negative bacilli (enteric organisms, and less commonly *Pseudomonas aeruginosa*) predominate. Fungal infections, mostly due to *Candida* spp., affect ~1 in 1000 kidney transplant [4], and manifest as surgical site infection, infected urinoma, graft abscess, and arteritis [4]. Positive blood culture for *Candida* early after kidney transplant should prompt the diagnosis of *Candida* arteritis since this is associated with very poor outcome and often requires nephrectomy [4–6].

Urinary Tract Infection (UTI)

UTI is the most common infection after kidney transplant, affecting 23–75 % of recipients [7]. It mostly occurs within the first 3–6 months after transplant [8]. These early onset UTIs are associated with a higher rate of pyelonephritis, septicemia, and recurrence or relapse than later onset UTIs. Of note, 60 % of bacteremia after transplant is related to the urinary tract, and 50 % of the bacteremic UTIs are associated with technical complications such as ureteral leaks or stricture, or with perinephric infection. UTIs, especially pyelonephritis, are associated with long-term graft function and outcomes [9–11].

Risk factors for UTI can be divided into recipient- and donor-specific, transplant procedure-specific, and posttransplant factors.

Recipient-Specific Factors

Risk factors that predispose to posttransplant UTI are similar to those in the general population and include old age, female sex, diabetes mellitus, pretransplant need of immunosuppression,

urinary abnormality including vesicoureteral reflux, and history of UTIs. Prolonged dialysis pretransplant and presence of polycystic kidney disease (especially when this was associated with pretransplant upper tract infection) are also at higher risk for UTIs after transplantation.

Donor Allograft-Specific Factors

Cadaveric allografts have been associated with higher rates of UTI and other complications than living donor allograft, as they are subjected to longer ischemic time, more severe ischemia-reperfusion injury and higher rate of delayed graft function. In addition, infected donor kidney, infected organ storage perfusate, and allograft trauma also predispose recipients to UTI.

Transplant Procedure-Related Factors

Retransplantation and transplant techniques also predispose to UTIs after transplant [12]. Renal transplants are generally performed in a heterotopic position, and the transplant ureter is anastomosed via an extravesical technique that may have a short anti-reflux tunnel [13]. Unfortunately, this does not eliminate vesicoureteric reflux and the subsequent risk of UTI. Intraoperative ureteral stents are being used at many centers to prevent urinary leakage and ureteral obstruction; this leads to an increase risk of UTI, especially when remains in place for more than 30 days. Lastly, an indwelling urinary catheter is routinely inserted during transplant surgery; the duration of indwelling catheter is directly related to the risk of UTI after transplant.

Posttransplant Factors

Graft dysfunction or rejection and excessive immunosuppression predispose to UTIs. Among the immunosuppressive agents, depleting antibodies like antithymocyte globulin and antimetabolites like azathioprine and mycophenolate mofetil have been associated with a higher risk of UTI.

UTI can present as asymptomatic bacteriuria, pyuria, acute cystitis, pyelonephritis, and septicemia [4, 10, 11, 13–15]. The diagnosis of UTI posttransplant might be difficult, since immunosuppression and the denervated allograft might mask clinical signs and symptoms of infection.

Pathogens causing UTIs in the kidney transplant recipients are similar to those from the general population, with *E. coli* as the most common. Other uropathogens include members of the *Enterobacteriaceae* group, *Pseudomonas aeruginosa*, *Enterococcus* spp., coagulase-negative *Staphylococcus*, and *Corynebacterium urealyticum*. Unusual bacteria with unknown virulence potential such as *Mycoplasma hominis*, *Ureaplasma urealyticum*, and *Lactobacillus* spp. can cause invasive infection in kidney transplant recipients. Over the past decade, there has been increasing reports of antimicrobial resistance among the uropathogens recovered from kidney transplant recipients.

Indeed, trimethoprim-sulfamethoxazole and fluoroquinolone-resistant uropathogens have been linked with prophylactic use of these agents [16]. More concerning, however, is the finding of multiple-drug-resistant organisms such as extended spectrum β lactamase-producing *Enterobacteriaceae* and vancomycin-resistant *Enterococcus* spp. in the urine of patients within 1 month of kidney transplantation [17].

Candida is the most common fungal pathogen causing UTI and affect ~11% of kidney transplant recipients. Diabetes mellitus appears to be the risk factor. Most of the patients with candiduria are asymptomatic, and to date, there have not been any reliable diagnostic tests that can differentiate colonization from true infection. *Candida* and *Aspergillus* are rarely associated with devastating complications such as pyelonephritis, candidemia, obstructing fungal ball at the ureterovesical junction and arteritis [18, 19].

The management of UTI relies on the clinical manifestations and onset from transplant (Table 2.1). All symptomatic UTIs should be treated, and the duration of treatment is dictated by the presence of upper tract disease, severity of infection or septicemia (Table 2.1). For asymptomatic bacteriuria during the first 1–3 months after transplant, although there have not been any controlled trials to influence treatment decision, most centers recommend antibiotic treatment, since this is the period when the allograft is particularly prone to injury, which adversely affects long-term allograft function [12], and UTI might not be clinically apparent due to denervation of the allograft and effect of immunosuppression. For late onset asymptomatic bacteriuria, treatment is recommended only for those with associated worsening renal function.

Antibiotic Prophylaxis

Several studies have clearly shown that antimicrobial prophylaxis significantly reduces the posttransplant infection rates for both living donor and cadaveric renal transplant [20]. The regimen used for prophylaxis, however, has not been well defined. Single drug regimen is as effective as multidrug regimens, and cefazolin is as effective as ceftriaxone in preventing SSIs. Based on data to date, the American Society of Health-System Pharmacists (ASHP) recommends cefazolin for renal transplant prophylaxis [20] (Table 2.2). For patients with β -lactam allergy, an agent effective against Gram positive cocci (clindamycin or vancomycin) given in combination with an agent effective against Gram negative rods (aztreonam or fluoroquinolone) are reasonable alternatives. The duration of prophylaxis is restricted to 24 h. Gentamicin might enhance the nephrotoxicity of other drugs used in transplant, and should be avoided.

Table 2.1 Management of UTI in kidney transplant recipients

	Recommendations	Note
<i>Asymptomatic bacteriuria</i>	There is no consensus recommendation on therapy for this category.	
Early (within 1–3 months of transplant)	Consider treatment based on culture and sensitivity. Duration: 5–7 days.	Because most UTIs are asymptomatic, a routine screening strategy of urine analysis and culture is performed at many transplant centers during the first 1–3 months after transplant.
Late (after 3 months)	No data to support antimicrobial therapy, but many centers prefer to treat patients with associated worsening in renal function.	Antimicrobial therapy beyond 1 month of transplant does not sustain sterilization of urine, prevent subsequent UTIs or improve graft function.
<i>Symptomatic UTI</i>		
	<ul style="list-style-type: none"> – Empiric treatment with broad spectrum antibiotic (based on patient's previous UTI history and local antibiogram), which can be tailored based on culture and sensitivity. – Consider removing ureteric stent. Duration: 7–10 days for lower tract infection, and 14–21 days for upper tract infection and septicemia. 	If patient does not respond, consider renal or perinephric abscess or emphysematous pyelonephritis.
Recurrent symptomatic UTI	Consider imaging (CT scan of kidney, cystoscopy, etc.). If no abnormality identified, consider treatment to 6 weeks	
Candiduria	Remove urinary catheter, stent. Treat with an antifungal agent (preferably an azole if susceptible) for symptomatic infection, persistent candiduria, neutropenia, or impending urologic procedure.	

Table 2.2 Antimicrobial prophylaxis recommendations for specific solid organ transplant organs

Organ transplant	ASHP recommendation (agents, duration)	Common practices at various transplant centers ^a	Notes
Kidney			
Antibacterial	Cefazolin ^a Duration: <24 h	Ampicillin-sulbactam 3 g IV Duration: <24 h	
Antifungal	Not recommended	Not recommended	
Pancreas or kidney-pancreas			
Antibacterial	Cefazolin ^a Duration: <24 h	Ampicillin-sulbactam 3 g IV or piperacillin-tazobactam 4.5 g IV Duration: 24–48 h	
Antifungal [98]	Fluconazole for patients at high risk for fungal infection ^c	Fluconazole 400 mg daily 2 weeks (1–4 weeks) ^c	Risk factor for candida infection: enteric drainage of the pancreas. ^c There have not been any controlled trials to support antifungal prophylaxis practice.
Liver			
Antibacterial	Piperacillin-tazobactam or cefotaxime plus ampicillin Duration: <24 h	Ampicillin-sulbactam 3 g IV	
Antifungal [98, 99]	Targeted prophylaxis: For patients at high risk for <i>Candida</i> infections: fluconazole Duration: up to 4 weeks For patients at high risk for mould infections: Liposomal amphotericin B (3–5 mg/kg/day) or an echinocandin Duration: up to 4 weeks or during initial hospital stay	Fluconazole 400 mg daily or echinocandin or a lipid formulation of amphotericin B Duration: up to 4 weeks or during initial hospital stay	<i>Risk factors for candida infections:</i> prolonged or repeat operation, retransplantation, renal failure, choledochojejunostomy, Candida colonization, requirement for transfusion of >40 units of blood products. <i>Risk factors for mould infections:</i> retransplantation, renal failure requiring renal replacement therapy, reoperation involving thoracic or abdominal cavity. There have not been any controlled trials to support antifungal prophylaxis practice.
Heart			
Antibacterial	Cefazolin <24 h	Cefazolin 1 g IV (or 2 g for weight >80 kg)	Patients with indwelling VAD might benefit from coverage of the infected microorganisms.

(continued)

Table 2.2 (continued)

Organ transplant	ASHP recommendation (agents, duration)	Common practices at various transplant centers ^a	Notes
Antifungal	Not addressed	Some centers offer targeted anti-mould prophylaxis: voriconazole or itraconazole 200 mg bid 50–150 days, or until risk factors resolve	Antifungal prophylaxis is recommended for the followings: isolation of <i>Aspergillus</i> species in respiratory tract cultures, reoperation, CMV disease, posttransplant hemodialysis, and existence of an episode of invasive aspergillosis in program 2 months before or after heart transplant. There have not been any controlled trials to support antifungal prophylaxis practice.
Lung			
Antibacterial	Cefazolin Duration: <24 h Regimen should be modified to cover for potential pathogens, pre- and posttransplant cultures from the recipients, as well as donor culture	Cefepime 2 g IV q12h or Aztreonam 2 g IV q8h + Vancomycin 1 g IV q12h Duration: 48–96 h (if sterility cultures are negative) ^b Regimen should be modified to cover for potential pathogens, pre- and posttransplant cultures from the recipients, as well as donor culture	If sterility cultures are positive for pathogenic bacteria, the duration of antimicrobial prophylaxis is extended to 7–10 days.
Antifungal	Targeted prophylaxis according to local fungal epidemiology, and risk factors for fungal infections	Voriconazole or itraconazole 200 mg BID or inhaled amphotericin B Duration: not known (up to 4 months)	Optimal antifungal prophylaxis is not known. AST Infectious Diseases Community of Practice recommends targeted prophylaxis for the following risk factors: (1) Pre, peri- or posttransplant colonization with <i>Aspergillus</i> ; or (2) ≥ 1 of the followings: induction with thymoglobulin or alemtuzumab, single lung transplant, acquired hypogammaglobulinemia. To date, there have not been any studies validating the efficacy of this approach.
Small bowel			
	Not discussed	Aztreonam 2 g IV q8h + vancomycin 1 g IV q12h + metronidazole 500 mg IV q8h or piperacillin-tazobactam 4.5 g IV q8h or a carbapenem Duration: 48–96 h or until surveillance enteroscopy demonstrates integrity of the intestinal allograft	
		Fluconazole 400 mg daily Duration: until surveillance enteroscopy demonstrates integrity of the intestinal allograft [98]	In some centers, anti-mould prophylaxis are targeted for: multivisceral transplant, abdominal reoperation, anastomotic site disruption, graft rejection, augmentation of immunosuppression

^aCommonly used at various transplant centers^bFor patients with b-lactam allergy, a combination of either vancomycin 1 g IV or clindamycin 600 mg IV with either aztreonam 2 g IV or a fluoroquinolone is an effective alternative^cIn the settings of high rates of non-*C. albicans* infection, either an echinocandin or a lipid formulation of amphotericin B is recommended

Pancreas or Kidney–Pancreas Transplant

Pancreas transplantation is considered a clean-contaminated surgery. Several factors predispose pancreas and kidney–pancreas transplant recipients to infections. First, individual's diabetes mellitus might be complicated by vascular insufficiency that leads to poor vascular flow and impaired wound healing after transplant. Second, renal failure pre-transplant is a risk factor for infection. Third, during transplant, spillage from the contaminated donor duodenum, which is used in the anastomosis between the pancreatic graft and either the intestine (enteric drainage) or bladder (bladder drainage) can contaminate the abdominal cavity.

Lastly, anastomotic leaks leading to intra-abdominal infection can occur after pancreas transplant. In general, the site of drainage of pancreas transplant has important implications for infectious complications: enteric drainage poses a risk of abdominal and graft infections, whereas bladder drainage poses a high risk for urinary tract infections.

SSIs

SSIs occur in 7–35 % of pancreas transplant recipients, and are more common after kidney–pancreas transplantation than kidney transplant alone [21]. Similar to kidney transplantation, superficial wound infections after kidney–pan-

creas transplantation are often caused by Gram positive cocci. Deep wound infections are more severe, and usually associated with intra-abdominal infections, and involve polymicrobial organisms of bacteria and *Candida* in ~50 % of the cases [22]. Donor's duodenum contamination, diabetes mellitus, and recipient's obesity predispose to SSIs [21, 23–25].

Intra-abdominal Infections

Intra-abdominal infections are among the most serious complications after pancreas transplant, occurring in ~5–10 % of patients. It is associated with graft loss and can be life threatening. Sources of infection includes donor duodenum duodenal leaks associated with enteric drainage, and graft inflammation or pancreatitis. The risk factors include donor age, obesity, and recipient's need for peritoneal dialysis and duration of dialysis pretransplant. Similar to SSIs, intra-abdominal infections after pancreas transplant are polymicrobial with bacteria and yeasts. Common organisms are *Enterococcus* spp., *Escherichia coli*, *Klebsiella* spp., and *Pseudomonas* spp. [22, 26]. ESBL-producing and carbapenem-resistant Gram negative rods have recently been reported [27]. Polymicrobial and fungal infections are associated with a higher mortality rate than monomicrobial bacterial infections. Fungal infection can lead to iliac artery mycotic aneurysm that might rupture [28]. Intra-abdominal infection is associated with a poor graft survival at 1-year, a high rate of graft removal at 50 % [26], and a mortality rate of 6–20 % [26, 29, 30].

UTIs

UTIs develop in a very high percentage of patients after pancreas or kidney–pancreas transplant, and 10–20 % of these have recurrent infections. Risk factors for UTI in pancreas transplant recipients are related to neurogenic bladder as a complication of diabetes mellitus, alkalization of the urine from bicarbonate in the pancreatic secretions among patients with bladder drainage, indwelling Foley catheters, and contamination from the donor's duodenum [31, 32]. The most common isolated organisms are *Enterococcus*, *Candida* spp., and *Pseudomonas aeruginosa* [17, 22, 31, 32].

Bacteremias

Bacteremias affect ~26 % of pancreas transplant patients, and are common within the first 3 weeks after transplant, especially among patients with enteric drainage [33]. Overall, bacteremia is associated with a higher mortality and graft loss, as well as higher rate of rejection [33].

Antimicrobial Prophylaxis

Due to the high rates of SSIs after pancreas transplant and their association with poor outcome, antimicrobial prophylaxis has become routine for pancreas transplant despite the lack of placebo-controlled studies. A single dose of cefazolin to donors and recipients appears effective in one nonrandomized study [34]. Another small randomized trial showed no significant impact of vancomycin given in conjunction with another antibacterial agent on infections due to Gram positive bacteria [35]. Given these findings, the ASHP recommend a single dose of cefazolin, or in the event of β -lactam allergy, combination of clindamycin or vancomycin with either aztreonam or a fluoroquinolone (Table 2.3). For patients with VRE colonization, an effective anti-VRE agent should be used (linezolid or tigecycline). Due to the high rate of candida infection in SSI, ASHP also recommends fluconazole prophylaxis for pancreatic transplant patients, especially those undergoing enteric drainage [20]. In settings of high prevalence of infections due to non-*C. albicans* spp., amphotericin B or caspofungin is a reasonable alternative antifungal agent.

Liver Transplant

Liver transplantation is a long and complex procedure, and at best, a clean-contaminated surgery. The most consistently identified risk factors for infections after liver transplantation are duration of surgery and retransplantation [36–38]. Other surgical risk predisposing to infections are previous hepatobiliary surgeries, intraoperative blood transfusions of >4 units, intra-peritoneal blood, and prolonged total ischemia time [36, 37, 39]. Roux-en-Y choledochojejunostomy is also a risk factor for transplant-related infections, as it predisposes to reflux of bowel flora into the biliary system. Lastly, complications from liver transplant, such as portal vein thrombosis, hepatic artery thrombosis, biliary leaks or stricture, affect 54–67 % of patients [38, 40–42], and predispose to infections.

SSIs

SSIs affect 4–48 % despite prophylaxis [43], and the majority of these are related to transplant technical problems. Peritonitis, bilomas, intra-hepatic abscesses, and cholangitis are most common infections, accounting for 27–48 % of all bacterial infections early after transplant [44]. Peritonitis and abscesses may complicate biliary anastomotic leaks, which are especially common after living donor transplant. Other risk factors include Roux-en-Y choledochojejunostomy, prolonged intraoperative time, human leukocyte antigen mismatches, low serum albumin levels, ascites, increased transfusion requirements, and severe obesity. *Bilomas* occurs in 12 % of patients after liver transplant in one study [45].

These are intrahepatic or perihepatic fluid collections that develop as complications of hepatic artery thrombosis or stenosis, and biliary necrosis, stricture, or leaks [40, 45, 46]. Broad-spectrum antibiotics and percutaneous drainage have varying degrees of success. If bilomas are associated with hepatic artery thrombosis, retransplantation is generally required.

SSIs are largely due to organisms colonizing the recipients' intestinal tract or skin pretransplant. MDR enteric Gram negative bacteria and *Enterococcus* (including vancomycin-resistant *E. faecium*), and *Candida* spp. are common infections in liver transplant recipients, especially in transplant centers using selective bowel decontamination [47]. *Candida* affects 53–68 % of liver recipients [48, 49], and manifests as intra-abdominal abscess, peritonitis, or candidemia. Risk factors for invasive candidiasis includes Roux-en-Y choledochojejunostomy, prolonged operative time (≥ 11 h) requiring >40 units of blood product, and *Candida* colonization or infection within 3 months of transplantation.

Antimicrobial Prophylaxis

As for pancreas transplant, due the high complexity of surgical procedure and high rates of infection, antibiotic prophylaxis has been a standard approach for liver transplantation despite the lack of controlled studies. ASHP recommends piperacillin-tazobactam or cefotaxime plus ampicillin [20], but many centers, including ours, use ampicillin-sulbactam (Table 2.2). For patients colonized with VRE, tigecycline is a reasonable alternative; some other centers add linezolid to the standard antibiotic regimen. For patients at high risk for *Candida* infection (choledochojejunostomy, known *Candida* colonization, and transfusion of >40 units of blood products), fluconazole may be considered for prophylaxis after transplant. Since invasive aspergillosis has the highest mortality in liver transplant recipients compared to other SOT recipients [50], some but not all transplant centers also consider an anti-mould prophylaxis with an echinocandin or an amphotericin B product for patients at high risk for mould infection (retransplantation, renal failure requiring renal replacement therapy, fulminant hepatic failure as indication for transplant, and intra-abdominal or thoracic reexploration within the first month after transplantation) [51].

Intestine or Multivisceral Transplant

Intestine or multivisceral transplantation is a complicated and difficult surgery that takes at least 8–10 h. It is considered as a contaminated, and sometime even dirty surgery.

As a consequence, the rates of infections associated with intestinal transplantation are higher than those reported with other organ transplant. Isolated intestinal transplant is associated with the lowest risk of infections, whereas multivisceral transplant is associated with the highest risk [52–56]. Indeed, over 90 % of multivisceral transplant patients have at least an infection after transplant, with the median of 5 infections per patient [54, 57–59]. This can be explained by pre-, peri-, and posttransplant risk factors. Pretransplant risk factors include patients' poor nutritional status (with associated secondary immunodeficiency), chronic total parenteral nutrition dependence (with associated risk for blood stream infection), underlying intra-abdominal anatomic abnormalities (with associated infections and translocation of bacteria), and presence of enterocutaneous fistula (with associated intra-abdominal infection and sepsis). Peritransplant factors include complexity of the surgical techniques in the setting of extensive intra-abdominal dissection, adhesions from previous abdominal surgery, potential intraoperative spillage, and the necessity of an intestinal anastomosis. In addition, complications and requirement for reoperation is high due to postoperative hemorrhage, vascular and biliary leaks, vascular and biliary obstructions, and intestinal perforation [53]. Intestinal allograft is an immunogenic organ which requires intensive immunosuppressive therapy [60]. Posttransplant risk factors include need for indwelling vascular catheters for temporary total parenteral nutrition, bacterial translocation arising from ischemia and reperfusion injury during the early transplant period, or from episodes of rejection. All these factors predispose to intra-abdominal abscess, peritonitis, and bacteremia [53]. The epidemiology and types of infections after intestinal and multivisceral transplantation are not as well described as for other organ transplant. Overall, bacteremia is the most common, followed by SSIs and intra-abdominal infections.

Bacteremia

Bacteremia occurs in >60 % of intestinal transplant patients [61, 62], and is more common in patients receiving a concomitant liver transplantation [63]. The sources of bacteremia are from indwelling vascular catheters and translocation of organisms from the GI tract in ~ 65 %. Bacteremia also originates from an infection from a deep-seated site or from other nosocomial infection. Bacteremia was polymicrobial in ~ 50 % of the cases [59], and the most common organisms were *Enterococcus* and *Staphylococcus* spp., followed by enteric Gram negative rods. *Candida* sp. accounted for ~ 3 % of bacteremia.

SSIs

SSIs, mostly intra-abdominal abscess and peritonitis, are the second most common infection after intestinal and multivisceral transplantation. *Staphylococcus* spp., *Enterococcus* spp., *Pseudomonas aeruginosa*, and members of the *Enterobacteriaceae* group are the most common causative agents. *Candida*, both *C. albicans* and non-*C. albicans* spp., are also important pathogens, affecting ~25% of patients [64]. The risk factors of deep-seated candida infections include use of broad spectrum antibiotics, use of induction immunosuppression for transplant, anastomotic leaks or intra-abdominal collections, the need for multiple abdominal surgical procedures, and the presence of a multivisceral graft [55]. Abscesses are not always accessible to percutaneous

drainage and may require laparotomy. In multivisceral transplant recipients, graft pancreatitis with bacterial or candida superinfection might also occur, in which case, the mortality rate is high.

Antimicrobial Prophylaxis

Since small bowel or multivisceral transplantation is a contaminated procedure, all patients should receive antimicrobial prophylaxis. There has not been any ASHP recommendation specifically for small bowel transplant (Table 2.3). The prophylaxis regimen should cover for the intestinal enteric flora; commonly used antimicrobial prophylaxis regimens include piperacillin-tazobactam, ampicillin-sulbactam,

Table 2.3 Prophylaxis against opportunistic infection

	Agent	Alternative	Note
<i>Pneumocystis jirovecii</i>	Trimethoprim (TMP)/sulfamethoxazole (SMX) 1 single strength (80 mg TMP) daily or 1 double strength (160 mg TMP) three times a week Duration: 6 months to 1 year. The duration is usually extended to beyond 1 year for lung transplant recipients (lifelong prophylaxis), patients receiving higher degrees of immunosuppression, or those with chronic viral infections	Aerosolized pentamidine 300 mg once a month Dapsone 100 mg daily ^a Atovaquone 1500 mg daily	TMP-SMX may also provide protection against <i>Toxoplasma</i> and <i>Listeria</i> species.
<i>Toxoplasma gondii</i>	For heart transplant, donor serology+/recipient serology–: TMP-SMX 1 single strength (80 mg TMP) daily or 1 double strength (160 mg TMP) three times a week Duration: Lifelong For recipient serology +: TMP/SMX as for PJP prophylaxis	Prophylactic regimen for high-risk patients is not known – Clindamycin-pyrimethamine has been used successfully – Other potential regimens include: sulfadiazine, dapsone, atovaquone, clindamycin in combination with pyrimethamine or primaquine	Patients at highest risk for toxoplasmosis are heart transplant recipients with pretransplant <i>Toxoplasma</i> serology negative who receive an organ from a donor with positive serology.
Cytomegalovirus [100]	Universal prophylaxis or preemptive therapy <i>Universal prophylaxis</i> : valganciclovir 900 mg PO daily Or ganciclovir 5 mg/kg IV daily IV Duration: 1. CMV D+/R–: 3–6 months for all organs except for lungs (12 months) 2. CMV R+: 3 months for all organs except for lungs (6 months) <i>Preemptive therapy</i> : weekly CMV PCR or pp65 antigenemia for 12 weeks after transplantation. For positive CMV threshold: treat with valganciclovir 900 mg PO BID or IV ganciclovir 5-mg/kg IV q12h until negative test		Patients at highest risk for CMV disease are those recipients with pretransplant CMV serology negative who receive an organ from a donor with positive serology (D+/R–); those with latent CMV infection who require treatment with antilymphocyte antibodies as a part of induction therapy or for graft rejection.
Herpes simplex (HSV) infection [101]	Acyclovir 400–800 mg PO BID or valacyclovir 500 PO BID for ≥1 month (Ganciclovir or valganciclovir is effective for HSV prophylaxis)		

Both universal prophylaxis and preemptive therapy strategies are equally effective in preventing CMV disease [102], but only universal prophylaxis reduces CMV organ disease among patients at highest risk (CMV D+/R– and induction with anti-lymphocyte antibodies), reduces rate of allograft rejection, bacterial and fungal infections, and death [103]

^aScreen for glucose 6-phosphatase dehydrogenase deficiency before prescribing this drug

and aztreonam + vancomycin with or without metronidazole. *Candida* prophylaxis with either fluconazole, an echinocandin, or an amphotericin B product should also be in the prophylaxis regimen. The duration of prophylaxis is not known, and is center-specific. Duration of 3–7 days is likely adequate, although many centers maintain antimicrobial prophylaxis until surveillance enteroscopy demonstrates integrity of the intestinal allograft (Table 2.3).

Heart Transplant

Heart transplant is considered a clean surgical procedure. However, the SSI rates after heart transplant are higher than those of other general cardiac surgeries, with the rates of superficial and deep SSIs after heart transplant ranging from 4 to 16 % and 2 to 35 %, respectively, compared with those of general cardiac surgeries of 8 % and 2 %, respectively [20, 65]. Even with antimicrobial prophylaxis, the rates of SSI remains at 5.8–8.8 %. Risk factors associated with SSI include: recipient age, BMI > 30 kg/m², female sex, previous cardiac procedure, receipt of ciprofloxacin as a single antibiotic prophylactic agent [66], and hemodynamic instability requiring inotropic support [20]. In addition, ventricular assist devices (VADs), especially when associated with infection, have been identified as risk factor for post-heart transplant SSI in several reports. Importantly, patients with device infection have significantly worse outcome in term of survival at 1 and 10 years after transplant. Although superficial SSIs are relatively easy to treat, deep SSIs such as mediastinitis and sternal wound infection, which affect 3–10 % of heart transplant recipients, are difficult to diagnose and treat, and prognosis is poor [67, 68]. Unlike in non-immunosuppressed patients, heart transplant patients with mediastinitis may not present with signs and symptoms of infection. For example, in one study, fever, chest wall erythema, or purulent discharge were present in only 30 % of patients, and leukocytosis in only 40 % of patients. Chest wall pain, in disproportion to sternotomy, appears to be the most common symptoms. Chest CT is sensitive in depicting mediastinal fluid collection or air. Once diagnosis is made, aggressive surgical debridement and appropriate antibiotic [69], followed by placement of vacuum-assisted drainage have been effective in controlling infections.

As with other cardiac surgeries, Gram positive organisms such as *S. aureus* and *Enterococcus faecalis* are primary causes of SSI after heart transplant. Gram negative bacilli, especially *E. coli* and *Acinetobacter*, have also been reported. Lastly, fungi, such as *Candida* and *Aspergillus*, occur much more commonly in heart transplant than other cardiac procedures. The rates of invasive aspergillosis range from 1 to 14 % [70, 71], and depend on whether or not the center employ antifungal prophylaxis.

Toxoplasmosis is a preventable, uncommon but fatal infection. Toxoplasmosis can occur after any organ transplant [72], but is most important after heart transplant because the *Toxoplasma* cysts are commonly found in muscle tissues. The highest risk group is transplanting a donor with *Toxoplasma* seropositivity into a seronegative recipient; the risk in this setting in the absence of prophylaxis is as high as 75 % [73]. The most common manifestations after transplant are myocarditis, brain abscess, pneumonia, empyema, or disseminated infection. Toxoplasmosis typically occurs between 25 and 195 days posttransplant. Primary infection transmitted by the donor organ is generally more severe than that due to reactivation of latent infection in the recipient [74].

Antimicrobial Prophylaxis

Although there has not been any randomized controlled trial to assess the need of antimicrobial prophylaxis, based on data of other types of cardiac procedures, antimicrobial prophylaxis is considered standard practice. ASHP recommends a single dose of cefazolin for all patients undergoing heart transplantation. For patients with a history of MRSA colonization or infection, vancomycin should be considered. For patients with a β -lactam allergy, vancomycin or clindamycin are reasonable alternatives. ASHP recommends <24 h of prophylaxis but many centers are given for 24–48 h. The duration of antimicrobial prophylaxis for patients who do not have their chest primarily closed is unclear; many centers continue prophylaxis until the chest is closed, but there is no evidence to support this practice.

Patients with an indwelling VAD or Extracorporeal Membrane Oxygenation (ECMO) and no history of device-related infections should receive the standard antimicrobial prophylaxis as patients with no devices. For those patients with previous history of device-related infections, antimicrobial prophylaxis should be effective against these organisms. The duration of antimicrobial prophylaxis might be longer than 24–48 h, based on the presence or absence of retained infections at the time of transplant.

Antifungal prophylaxis in heart transplant is a controversial issue. Although universal antifungal prophylaxis with either itraconazole or inhaled amphotericin B during the first 3 months of transplant is safe and effective, considering the low incidence of invasive aspergillosis after heart transplant recipients, targeted prophylaxis is widely preferred [75]. The major indications for targeted antifungal prophylaxis are: retransplantation, reoperation, end-stage renal disease requiring hemodialysis, Cytomegalovirus disease and existence of another patient with invasive aspergillosis in the heart transplant program within 3 months of the transplant procedure [76]. The typical recommended duration of antifungal prophylaxis is 3 weeks after the resolution of the risk factors.

Lung Transplant

Lung transplant is considered a clean-contaminated surgery. Infections are the most common complications after lung transplant, and account for ~25 % of death within the first year. Lung transplant is particularly at risk for respiratory tract infection because of the blunted cough from allograft denervation, impaired mucociliary clearance due to ischemic reperfusion injury to the bronchial mucosa, and exposure of the allograft to the external environment. In addition, since there is no direct blood supply to the donor bronchus and bronchial anastomosis, and circulation to this area depends on collateral circulation from the pulmonary arteries, airway ischemia is a serious problem early after lung transplantation, leading to airway complications such as bronchial stenosis, dehiscence, malacia, and necrosis; these may in turn facilitate colonization with subsequent infection by bacterial or fungal pathogens.

Tracheobronchitis and Endobronchial Infection

Tracheobronchitis and endobronchial infection are unique forms of airway infections that typically develop within the first 3 months of lung transplantation. The diagnosis is suggested by bronchoscopic findings of airway purulence, pseudomembrane, endobronchial plaques with or without necrosis or dehiscence, and confirmed by culture and histopathology. The actual rate of airway infection is not known, because it is often incorporated under “lung infection.” Both bacteria (like *S. aureus*, *P. aeruginosa*, and *Burkholderia* spp.) and fungi (*Candida* spp. and pathogenic moulds) have been implicated in airway infections.

Pneumonia

Pneumonia is by far the leading cause of pulmonary infection, and affects 10–20 % of patients within the first 30 days of lung transplantation despite antibiotic prophylaxis [77]. Organisms causing pneumonia arise either from the recipient’s or donor’s respiratory tract, or the hospital environment. Even after the source of infection in the native lungs is removed during lung transplantation, the patients might continue to be colonized with their endogenous flora, since the organisms can persist in the native upper airways and/or sinuses. Patients with cystic fibrosis are at particular risk for severe pneumonia, because they are chronically colonized and/or infected with multiple-drug-resistant bacteria such as *Pseudomonas aeruginosa*, *Burkholderia* spp., *Achromobacter*, and *Alcaligenes*, as well as methicillin-resistant *Staphylococcus aureus*. *Burkholderia cenocepacia* causes significant problems and leads to very poor outcome among cystic fibrosis patients posttransplant due its unique multidrug-resistant patterns; for this reason, colonization or infection due to this specific organism is con-

sidered a strong relative contraindication for lung transplant at many centers. It is important to note that although ~60 % of donor respiratory tracts are colonized with organisms, the presence of these organisms does not necessarily predict pneumonia in lung transplant recipients. Several studies have shown that, in the setting of appropriate antibiotic prophylaxis, 6–12 % of lung recipients develop pneumonia from organisms transmitted from the donor [77, 78].

Lung transplant recipients have a higher rate of invasive fungal infections than other organ transplant recipients. *Aspergillus* (*A. fumigatus* most common, followed by *A. flavus*, *A. terreus*) is the most common cause of fungal infection following lung transplantation [79]. Pretransplant colonization or a positive intraoperative culture with *Aspergillus* increases risk of invasive *Aspergillus* infection after transplant [80]. Other risk factors predisposing to invasive fungal infection include airway ischemia, receipt of a single lung transplant, fungal sinusitis, neutropenia, hypogammaglobulinemia, receipt of thymoglobulin or augmentation of immunosuppression for cellular rejection, intercurrent viral infections (CMC, respiratory viruses, etc.), renal failure requiring hemodialysis, and mechanical intervention of the airway (such as airway stenting or ballooning) [81].

In the early period after lung transplant, airway disease due to *Aspergillus* (tracheobronchial aspergillosis) is more common than parenchymal disease (pneumonia) [82, 83]. Tracheobronchial aspergillosis occurs in ~5 % of all lung transplant patients. Cystic fibrosis patients with pretransplant *Aspergillus* colonization are at risk for developing tracheobronchial aspergillosis and anastomotic complications despite antifungal prophylaxis [84–86]. Airway aspergillosis has a wide spectrum of clinical manifestations, ranging from simple tracheobronchitis, plaque-like necrotic endobronchial lesions, to ulcerative tracheobronchitis and to necrotizing pseudomembranous formation. Tracheobronchial aspergillosis can occur alone, or in conjunction with parenchymal disease. It is sometimes difficult to differentiate from ischemic reperfusion injury, and the diagnosis relies on histopathology and microbiology for differentiation. Treatment of tracheobronchial aspergillosis involves systemic antifungal therapy in conjunction with inhaled antifungal with or without debridement and stent placement [87–90]. In this early transplant period when the anastomotic site is devascularized, adjunctive inhaled antifungal agent might be valuable since parenteral therapy might not achieve therapeutic concentrations. Duration of therapy is not known, but the typical approach is to continue antifungal therapy until the lesions are cleared on bronchoscopy, or for at least 3 months. In general, *Aspergillus* tracheobronchitis has a better response rate to antifungal therapy (71–82 %) than pulmonary disease (26–41 %) [87].

Fungi other than *Aspergillus* spp. such as *Scedosporium*, *Fusarium*, and the agents of mucormycosis and phaeohyphomycosis have been increasingly recognized as important

pathogens in lung transplantation, causing both airway and pulmonary disease [91]. Diseases due to these non-*Aspergillus* moulds are associated with mortality rate up to 80%.

SSIs

SSIs affect 5–11% of lung transplant recipients, rates which are higher than the 1–2% rate reported for cardiothoracic surgery. Superficial SSI is of minor clinical significance. Deep SSIs, on the other hand, have been linked with prolonged hospitalization stay, high cost, and poor long-term outcome [86, 92]. Pleural empyema is the most common, followed by surgical wound infections; mediastinitis, sternal osteomyelitis, and pericarditis are rare. Of note, mediastinitis and sternal infections were not observed among patients undergoing minimally invasive lung transplantation [92].

Empyema occurs in 3–8% of patients after lung transplantation [86, 93, 94]. Lung transplant recipients are at risk for empyema because the organisms within the infected native lungs (as in cases of cystic fibrosis or bronchiectasis) can spill into the chest cavity during lung explantation. Second, development of pleural effusion is almost universal after lung transplant due to increased alveolar capillary permeability and disruption of lymphatic channel, and the effusion might get infected. Lastly, indwelling chest tubes might also predispose to infection. Empyema usually occurs within the first 6 months following transplant [86]. Earlier series associated empyema with increased patient mortality [86]. In our more recent series, however, empyema is associated with less morbidity and mortality than other SSIs [92]. Management requires surgical drainage or placement of a chest tube drain in conjunction with effective antibiotic. In some cases, empyema may result in significant scarring which requires decortication [95].

The microbiology is diverse. Gram-positive (*S. aureus*) and Gram-negative (*P. aeruginosa*, *E. coli*, *Klebsiella* spp., and *Acinetobacter*) are the predominant pathogens, but other atypical pathogens including *Mycobacterium abscessus*, *Mycoplasma hominis*, and *Lactobacillus* sp. have also been reported. Importantly, in one study, 23% of SSIs were due to pathogens colonizing recipients' native lungs at time of lung transplantation, suggesting surgical seeding as a source.

Antimicrobial Prophylaxis

Antimicrobial prophylaxis for lung transplantation is routinely administered despite the lack of randomized controlled trials. ASHP recommends a single dose of cefazolin, but this might not be sufficient, especially for patients with suppurative lung diseases or those with chronic lung infections. Lung transplant centers are using broader spectrum antimicrobial agents. The general prophylaxis regimen recommendation is based on: (1) local antibiogram of common Gram-positive and

Gram-negative pathogens associated with nosocomial infection, (2) pathogens previously recovered from a given patient and their susceptibility, and (3) pathogens recently recovered from the donor's respiratory (and/or blood) culture. Many transplant centers use an anti-pseudomonal antibiotic (cefepime, ceftazidime, piperacillin-tazobactam, or aztreonam); vancomycin is added for patients known to be previously colonized or infected with MRSA. Routine respiratory tract cultures of the donor and recipient (called sterility cultures) are performed at the time of transplant, the result of which will dictate the subsequent antimicrobial regimen. The duration of prophylaxis varies per centers. At our center, we stop antimicrobial agents after 3 days if the sterility cultures are negative. If the sterility cultures are positive, the antimicrobial agent(s) will be modified according to susceptibility data, and continue(s) for 7 days; for organisms such as *Pseudomonas aeruginosa* or MRSA, the antibiotics are continued for 14 days. The duration of antibiotics prophylaxis for patients with cystic fibrosis might be longer. Although the role of inhaled aminoglycosides has not been systematically studied, its use has become popular among lung transplant recipients with cystic fibrosis or purulent lung disease due to multidrug-resistant Gram-negative bacteria prior to transplant.

Although there are no randomized controlled trials to advocate the use of antifungal prophylaxis in lung transplantation, this practice is commonly used among lung transplant centers [96], as evidence exists that antifungal prophylaxis decreased the incidence of invasive aspergillosis [79]. Common prophylaxis regimens include a systemic antifungal agent (voriconazole or itraconazole) or inhaled amphotericin. Inhaled amphotericin B has the advantage of direct delivery to the at-risk anastomotic site. The oral suspension of posaconazole is not commonly used because of problems with absorption after transplant (protein pump inhibitor use, requirement for nasogastric tube feeding, poor appetite after transplant, etc.); the delayed-release tablet provides better bioavailability than the suspension and might become a preferred option if posaconazole is considered. The optimal duration of prophylaxis is not known. Although prophylaxis is efficacious in preventing invasive fungal infections, late onset fungal disease might occur after the antifungal is stopped. The safety of prolonged duration of antifungal prophylaxis is not known, and there have been links between prolonged voriconazole use and the development of squamous cell skin cancer [97]. Clearly randomized controlled trials are needed to define optimal regimens for efficacy and safety.

Standard Prophylaxis Against Opportunistic Pathogens

In addition to specific organ transplant perioperative prophylaxis, all solid organ transplant recipients need to receive prophylaxis against opportunistic infections. Please refer to Table 2.3 for specific recommendations.

In conclusion, infections occurring after solid organ transplantation reflect the intricate relationship between the net state of immunosuppression and environmental exposure. Familiarity with the epidemiology, risk factors, and time line of posttransplant infections, and surgical techniques and complications is necessary to design appropriate antimicrobial prophylaxis. Preventing infections is the most important method for improving both short-term and long-term morbidity and mortality of organ transplant recipients.

References

1. Fishman JA. Infection in solid-organ transplant recipients. *N Engl J Med*. 2007;357:2601–14.
2. Owens CD, Stoessel K. Surgical site infections: epidemiology, microbiology and prevention. *J Hosp Infect*. 2008;70 Suppl 2:3–10.
3. Humar A, Matas AJ. Surgical complications after kidney transplantation. *Semin Dial*. 2005;18:505–10.
4. Albano L, Bretagne S, Mamzer-Bruneel MF, et al. Evidence that graft-site candidiasis after kidney transplantation is acquired during organ recovery: a multicenter study in France. *Clin Infect Dis*. 2009;48:194–202.
5. Laouad I, Buchler M, Noel C, et al. Renal artery aneurysm secondary to *Candida albicans* in four kidney allograft recipients. *Transplant Proc*. 2005;37:2834–6.
6. Potti A, Danielson B, Sen K. “True” mycotic aneurysm of a renal artery allograft. *Am J Kidney Dis*. 1998;31:E3.
7. Parasuraman R, Julian K. AST Infectious Diseases Community of Practice. Urinary tract infections in solid organ transplantation. *Am J Transplant*. 2013;13 Suppl 4:327–36.
8. Abbott KC, Oliver III JD, Hypolite I, et al. Hospitalizations for bacterial septicemia after renal transplantation in the United States. *Am J Nephrol*. 2001;21:120–7.
9. Abbott KC, Swanson SJ, Richter ER, et al. Late urinary tract infection after renal transplantation in the United States. *Am J Kidney Dis*. 2004;44:353–62.
10. Chuang P, Parikh CR, Langone A. Urinary tract infections after renal transplantation: a retrospective review at two US transplant centers. *Clin Transplant*. 2005;19:230–5.
11. Fujita S, Watanabe J, Reed AI, et al. Case of emphysematous pyelonephritis in a renal allograft. *Clin Transplant*. 2005;19:559–62.
12. Saemann M, Horl WH. Urinary tract infection in renal transplant recipients. *Eur J Clin Invest*. 2008;38 Suppl 2:58–65.
13. de Souza RM, Olsburgh J. Urinary tract infection in the renal transplant patient. *Nat Clin Pract Nephrol*. 2008;4:252–64.
14. Schmaldienst S, Dittrich E, Horl WH. Urinary tract infections after renal transplantation. *Curr Opin Urol*. 2002;12:125–30.
15. Chuang YW, Chen CH, Cheng CH, et al. Severe emphysematous pyelonephritis in a renal allograft: successful treatment with percutaneous drainage and antibiotics. *Clin Nephrol*. 2007;68:42–6.
16. Rafat C, Vimont S, Ancel PY, et al. Ofloxacin: new applications for the prevention of urinary tract infections in renal graft recipients. *Transpl Infect Dis*. 2011;13:344–52.
17. Kawecki D, Kwiatkowski A, Michalak G, et al. Urinary tract infections in the early posttransplant period after simultaneous pancreas-kidney transplantation. *Transplant Proc*. 2009;41:3148–50.
18. Fisher JF, Sobel JD, Kauffman CA, Newman CA. *Candida* urinary tract infections—treatment. *Clin Infect Dis*. 2011;52 Suppl 6:S457–66.
19. Franco A, Prados MC, Perdiguero M, Olivares J. Fungus ball: a cause of early obstructive uropathy in renal transplantation. *Clin Nephrol*. 1992;38:294.
20. Bratzler DW, Dellinger EP, Olsen KM, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. *Surg Infect (Larchmt)*. 2013;14:73–156.
21. Eckhoff DE, Sollinger HW. Surgical complications after simultaneous pancreas-kidney transplant with bladder drainage. *Clin Transpl*. 1993;185–91.
22. Humar AA. Risks and epidemiology of infections after pancreas or kidney-pancreas transplantation. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2010.
23. Humar A, Kandaswamy R, Granger D, Gruessner RW, Gruessner AC, Sutherland DE. Decreased surgical risks of pancreas transplantation in the modern era. *Ann Surg*. 2000;231:269–75.
24. Humar A, Ramcharan T, Kandaswamy R, Gruessner RW, Gruessner AG, Sutherland DE. The impact of donor obesity on outcomes after cadaver pancreas transplants. *Am J Transplant*. 2004;4:605–10.
25. Humar A, Ramcharan T, Kandaswamy R, et al. Pancreas after kidney transplants. *Am J Surg*. 2001;182:155–61.
26. Benedetti E, Gruessner AC, Troppmann C, et al. Intra-abdominal fungal infections after pancreatic transplantation: incidence, treatment, and outcome. *J Am Coll Surg*. 1996;183:307–16.
27. Kawecki D, Kwiatkowski A, Michalak G, et al. Surgical site infections in the early posttransplant period after simultaneous pancreas-kidney transplantation. *Transplant Proc*. 2009;41:3143–7.
28. Verni MP, Leone JP, DeRoover A. Pseudoaneurysm of the Y-graft/iliac artery anastomosis following pancreas transplantation: a case report and review of the literature. *Clin Transplant*. 2001;15:72–6.
29. Troppmann C. Complications after pancreas transplantation. *Curr Opin Organ Transplant*. 2010;15:112–8.
30. Troppmann C, Gruessner AC, Dunn DL, Sutherland DE, Gruessner RW. Surgical complications requiring early relaparotomy after pancreas transplantation: a multivariate risk factor and economic impact analysis of the cyclosporine era. *Ann Surg*. 1998;227:255–68.
31. Sollinger HW, Messing EM, Eckhoff DE, et al. Urological complications in 210 consecutive simultaneous pancreas-kidney transplants with bladder drainage. *Ann Surg*. 1993;218:561–8. discussion 8–70.
32. Sollinger HW, Sasaki TM, D’Alessandro AM, et al. Indications for enteric conversion after pancreas transplantation with bladder drainage. *Surgery*. 1992;112:842–5. discussion 5–6.
33. Singh RP, Farney AC, Rogers J, et al. Analysis of bacteremia after pancreatic transplantation with enteric drainage. *Transplant Proc*. 2008;40:506–9.
34. Barone GW, Hudec WA, Sailors DM, Ketel BL. Prophylactic wound antibiotics for combined kidney and pancreas transplants. *Clin Transplant*. 1996;10:386–8.
35. Pfundstein J, Roghmann MC, Schwalbe RS, et al. A randomized trial of surgical antimicrobial prophylaxis with and without vancomycin in organ transplant patients. *Clin Transplant*. 1999;13:245–52.
36. George DL, Arnow PM, Fox AS, et al. Bacterial infection as a complication of liver transplantation: epidemiology and risk factors. *Rev Infect Dis*. 1991;13:387–96.
37. Hadley S, Samore MH, Lewis WD, Jenkins RL, Karchmer AW, Hammer SM. Major infectious complications after orthotopic liver transplantation and comparison of outcomes in patients receiving cyclosporine or FK506 as primary immunosuppression. *Transplantation*. 1995;59:851–9.
38. Kusne S, Dummer JS, Singh N, et al. Infections after liver transplantation. An analysis of 101 consecutive cases. *Medicine (Baltimore)*. 1988;67:132–43.

39. Hau T, Hoffman R, Simmons RL. Mechanisms of the adjuvant effect of hemoglobin in experimental peritonitis. I. In vivo inhibition of peritoneal leukocytosis. *Surgery*. 1978;83:223–9.
40. Huprikar S. Update in infectious diseases in liver transplant recipients. *Clin Liver Dis*. 2007;11:337–54.
41. Asensio A, Ramos A, Cuervas-Mons V, et al. Effect of antibiotic prophylaxis on the risk of surgical site infection in orthotopic liver transplant. *Liver Transpl*. 2008;14:799–805.
42. Paya CV, Hermans PE, Washington II JA, et al. Incidence, distribution, and outcome of episodes of infection in 100 orthotopic liver transplantations. *Mayo Clin Proc*. 1989;64:555–64.
43. Hollenbeak CS, Alfrey EJ, Sheridan K, Burger TL, Dillon PW. Surgical site infections following pediatric liver transplantation: risks and costs. *Transpl Infect Dis*. 2003;5:72–8.
44. Reid GE, Grim SA, Sankary H, Benedetti E, Oberholzer J, Clark NM. Early intra-abdominal infections associated with orthotopic liver transplantation. *Transplantation*. 2009;87:1706–11.
45. Said A, Safdar N, Lucey MR, et al. Infected bilomas in liver transplant recipients, incidence, risk factors and implications for prevention. *Am J Transplant*. 2004;4:574–82.
46. Safdar N, Said A, Lucey MR, et al. Infected bilomas in liver transplant recipients: clinical features, optimal management, and risk factors for mortality. *Clin Infect Dis*. 2004;39:517–25.
47. Singh N, Gayowski T, Rihs JD, Wagener MM, Marino IR. Evolving trends in multiple-antibiotic-resistant bacteria in liver transplant recipients: a longitudinal study of antimicrobial susceptibility patterns. *Liver Transpl*. 2001;7:22–6.
48. Pappas PG, Silveira FP. Candida in solid organ transplant recipients. *Am J Transplant*. 2009;9 Suppl 4:S173–9.
49. Pappas PG, Alexander BD, Andes DR, et al. Invasive fungal infections among organ transplant recipients: results of the Transplant-Associated Infection Surveillance Network (TRANSNET). *Clin Infect Dis*. 2010;50:1101–11.
50. Neofytos D, Fishman JA, Horn D, et al. Epidemiology and outcome of invasive fungal infections in solid organ transplant recipients. *Transpl Infect Dis*. 2010;12:220–9.
51. Singh N, Husain S. Invasive aspergillosis in solid organ transplant recipients. *Am J Transplant*. 2009;9 Suppl 4:S180–91.
52. Ghanekar A, Grant D. Small bowel transplantation. *Curr Opin Crit Care*. 2001;7:133–7.
53. Reyes J, Abu-Elmagd K, Tzakis A, et al. Infectious complications after human small bowel transplantation. *Transplant Proc*. 1992;24:1249–50.
54. Tzakis AG, Kato T, Levi DM, et al. 100 multivisceral transplants at a single center. *Ann Surg*. 2005;242:480–90. discussion 91–3.
55. Timpone Jr JG, Girlanda R, Rudolph L, Fishbein TM. Infections in intestinal and multivisceral transplant recipients. *Infect Dis Clin North Am*. 2013;27:359–77.
56. Primeggia J, Matsumoto CS, Fishbein TM, Karacki PS, Fredette TM, Timpone JG. Infection among adult small bowel and multivisceral transplant recipients in the 30-day postoperative period. *Transpl Infect Dis*. 2013;15:441–8.
57. Guaraldi G, Cocchi S, Codeluppi M, et al. Outcome, incidence, and timing of infectious complications in small bowel and multivisceral organ transplantation patients. *Transplantation*. 2005;80:1742–8.
58. Loinaz C, Kato T, Nishida S, et al. Bacterial infections after intestine and multivisceral transplantation. The experience of the University of Miami (1994–2001). *Hepatogastroenterology*. 2006;53:234–42.
59. Loinaz C, Kato T, Nishida S, et al. Bacterial infections after intestine and multivisceral transplantation. *Transplant Proc*. 2003;35:1929–30.
60. Fishbein TM. Intestinal transplantation. *N Engl J Med*. 2009;361:998–1008.
61. Sigurdsson L, Reyes J, Kocoshis SA. Intestinal transplantation in children. *Curr Gastroenterol Rep*. 1999;1:259–65.
62. Sigurdsson L, Reyes J, Kocoshis SA, Mazariegos G, Abu-Elmagd K, Green M. Bacteremia after intestinal transplantation in children correlates temporally with rejection or gastrointestinal lymphoproliferative disease. *Transplantation*. 2000;70:302–5.
63. Akhter K, Timpone J, Matsumoto C, Fishbein T, Kaufman S, Kumar P. Six-month incidence of bloodstream infections in intestinal transplant patients. *Transpl Infect Dis*. 2012;14:242–7.
64. Florescu DF, Islam KM, Grant W, et al. Incidence and outcome of fungal infections in pediatric small bowel transplant recipients. *Transpl Infect Dis*. 2010;12:497–504.
65. Montoya JG, Giraldo LF, Efron B, et al. Infectious complications among 620 consecutive heart transplant patients at Stanford University Medical Center. *Clin Infect Dis*. 2001;33:629–40.
66. Ramos A, Asensio A, Munez E, et al. Incisional surgical infection in heart transplantation. *Transpl Infect Dis*. 2008;10:298–302.
67. Carrier M, Perrault LP, Pellerin M, et al. Sternal wound infection after heart transplantation: incidence and results with aggressive surgical treatment. *Ann Thorac Surg*. 2001;72:719–23. discussion 23–4.
68. Zuckermann A, Barten MJ. Surgical wound complications after heart transplantation. *Transpl Int*. 2011;24:627–36.
69. Chou NK, Wang JL, Chi NH, et al. Surgical treatment of mediastinitis after cardiac transplantation. *Transplant Proc*. 2008;40:2629–30.
70. Munoz P, Ceron I, Valerio M, et al. Invasive aspergillosis among heart transplant recipients: a 24-year perspective. *J Heart Lung Transplant*. 2014;33:278–88.
71. Zaoutis TE, Webber S, Naftel DC, et al. Invasive fungal infections in pediatric heart transplant recipients: incidence, risk factors, and outcomes. *Pediatr Transplant*. 2011;15:465–9.
72. Fernandez-Sabe N, Cervera C, Farinas MC, et al. Risk factors, clinical features, and outcomes of toxoplasmosis in solid-organ transplant recipients: a matched case-control study. *Clin Infect Dis*. 2012;54:355–61.
73. Fishman JA. Pneumocystis carinii and parasitic infections in transplantation. *Infect Dis Clin North Am*. 1995;9:1005–44.
74. Derouin F, Pelloux H, ESCMID Study Group on Clinical Parasitology. Prevention of toxoplasmosis in transplant patients. *Clin Microbiol Infect*. 2008;14:1089–101.
75. Tissot F, Pascual M, Hullin R, et al. Impact of targeted antifungal prophylaxis in heart transplant recipients at high risk for early invasive fungal infection. *Transplantation*. 2014;97(11):1192–7.
76. Pelaez T, Munoz P, Guinea J, et al. Outbreak of invasive aspergillosis after major heart surgery caused by spores in the air of the intensive care unit. *Clin Infect Dis*. 2012;54:e24–31.
77. Aguilar-Guisado M, Givalda J, Ussetti P, et al. Pneumonia after lung transplantation in the RESITRA Cohort: a multicenter prospective study. *Am J Transplant*. 2007;7:1989–96.
78. Ruiz I, Gavalda J, Monforte V, et al. Donor-to-host transmission of bacterial and fungal infections in lung transplantation. *Am J Transplant*. 2006;6:178–82.
79. Minari A, Husni R, Avery RK, et al. The incidence of invasive aspergillosis among solid organ transplant recipients and implications for prophylaxis in lung transplants. *Transpl Infect Dis*. 2002;4:195–200.
80. Luong ML, Chaparro C, Stephenson A, et al. Pretransplant Aspergillus colonization of cystic fibrosis patients and the incidence of post-lung transplant invasive aspergillosis. *Transplantation*. 2014;97:351–7.
81. Schaenman JM. Is universal antifungal prophylaxis mandatory in lung transplant patients? *Curr Opin Infect Dis*. 2013;26:317–25.
82. Gordon SM, Avery RK. Aspergillosis in lung transplantation: incidence, risk factors, and prophylactic strategies. *Transpl Infect Dis*. 2001;3:161–7.

83. Kramer MR, Denning DW, Marshall SE, et al. Ulcerative tracheo-bronchitis after lung transplantation. A new form of invasive aspergillosis. *Am Rev Respir Dis*. 1991;144:552–6.
84. Avery RK. Prophylactic strategies before solid-organ transplantation. *Curr Opin Infect Dis*. 2004;17:353–6.
85. Helmi M, Love RB, Welter D, Cornwell RD, Meyer KC. Aspergillus infection in lung transplant recipients with cystic fibrosis: risk factors and outcomes comparison to other types of transplant recipients. *Chest*. 2003;123:800–8.
86. Nunley DR, Grgurich WF, Keenan RJ, Dauber JH. Empyema complicating successful lung transplantation. *Chest*. 1999;115:1312–5.
87. Mehrad B, Paciocco G, Martinez FJ, Ojo TC, Iannettoni MD, Lynch III JP. Spectrum of Aspergillus infection in lung transplant recipients: case series and review of the literature. *Chest*. 2001;119:169–75.
88. Horvath J, Dummer S, Loyd J, Walker B, Merrill WH, Frist WH. Infection in the transplanted and native lung after single lung transplantation. *Chest*. 1993;104:681–5.
89. Yeldandi V, Laghi F, McCabe MA, et al. Aspergillus and lung transplantation. *J Heart Lung Transplant*. 1995;14:883–90.
90. Westney GE, Kesten S, De Hoyos A, Chapparro C, Winton T, Maurer JR. Aspergillus infection in single and double lung transplant recipients. *Transplantation*. 1996;61:915–9.
91. Bhaskaran A, Hosseini-Moghaddam SM, Rotstein C, Husain S. Mold infections in lung transplant recipients. *Semin Respir Crit Care Med*. 2013;34:371–9.
92. Shields RK, Clancy CJ, Mincis LR, et al. Epidemiology and outcomes of deep surgical site infections following lung transplantation. *Am J Transplant*. 2013;13:2137–45.
93. Ferrer J, Roldan J, Roman A, et al. Acute and chronic pleural complications in lung transplantation. *J Heart Lung Transplant*. 2003;22:1217–25.
94. Herridge MS, de Hoyos AL, Chapparro C, Winton TL, Kesten S, Maurer JR. Pleural complications in lung transplant recipients. *J Thorac Cardiovasc Surg*. 1995;110:22–6.
95. Boffa DJ, Mason DP, Su JW, et al. Decortication after lung transplantation. *Ann Thorac Surg*. 2008;85:1039–43.
96. Neoh CF, Snell GI, Kotsimbos T, et al. Antifungal prophylaxis in lung transplantation—a world-wide survey. *Am J Transplant*. 2011;11:361–6.
97. Williams K, Mansh M, Chin-Hong P, Singer J, Arron ST. Voriconazole-associated cutaneous malignancy: a literature review on photocarcinogenesis in organ transplant recipients. *Clin Infect Dis*. 2014;58:997–1002.
98. Silveira FP, Kusne S, AST Infectious Diseases Community of Practice. Candida infections in solid organ transplantation. *Am J Transplant*. 2013;13 Suppl 4:220–7.
99. Singh N, Husain S, AST Infectious Diseases Community of Practice. Aspergillosis in solid organ transplantation. *Am J Transplant*. 2013;13 Suppl 4:228–41.
100. Razonable RR, Humar A, AST Infectious Diseases Community of Practice. Cytomegalovirus in solid organ transplantation. *Am J Transplant*. 2013;13 Suppl 4:93–106.
101. Wilck MB, Zuckerman RA, AST Infectious Diseases Community of Practice. Herpes simplex virus in solid organ transplantation. *Am J Transplant*. 2013;13 Suppl 4:121–7.
102. Small LN, Lau J, Snyderman DR. Preventing post-organ transplantation cytomegalovirus disease with ganciclovir: a meta-analysis comparing prophylactic and preemptive therapies. *Clin Infect Dis*. 2006;43:869–80.
103. Kalil AC, Levitsky J, Lyden E, Stoner J, Freifeld AG. Meta-analysis: the efficacy of strategies to prevent organ disease by cytomegalovirus in solid organ transplant recipients. *Ann Intern Med*. 2005;143:870–80.

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