Chapter 11
The Role of Infections in BOS

Robin K. Avery

Abstract Background: Infectious agents, particularly cytomegalovirus (CMV), have long been considered to be potential triggers for BOS, although the exact magnitude of the role of infections and the mechanisms thereof remain an area of active research. Methods: This chapter will review previous literature and newer results concerning the possible roles of CMV, other herpesviruses, community-acquired respiratory viruses, bacteria (including *Pseudomonas*, other gram-negative, gram-positive, and atypical organisms), and fungi, including colonization as well as invasive infection. Results: The text reviews and evaluates the body of literature supporting a role for these infectious agents as risk factors for BOS and time to BOS. Changing patterns of infection over time are taken into account, and studies that have shown an association between BOS (or lack thereof) and CMV are reviewed. Strategies for prevention or early treatment of infections are discussed as potential means of preserving allograft function long term. Immunizations, stringent infection-control practices, and antimicrobial treatment including newer therapies will be discussed. Conclusion: In addition to the classic literature that has focused on CMV, an expanding spectrum of infectious organisms has been implicated as possible risk factors for BOS. Increasing knowledge of the impact of long-term antiviral suppression, prophylaxis, and outcomes of early therapy will help guide future recipient management.

Keywords Infection • Cytomegalovirus • Bacterial • *Pseudomonas* • Gram-positive • Gram-negative • Fungal • Prophylaxis

R.K. Avery, M.D. (✉)
Division of Infectious Disease (Transplant/Oncology), Johns Hopkins Hospital, 1830 East Monument Street, No. 434, Baltimore, MD 21205, USA
e-mail: ravery4@jhmi.edu

K.C. Meyer and A.R. Glanville (eds.), *Bronchiolitis Obliterans Syndrome in Lung Transplantation*, Respiratory Medicine 8, DOI 10.1007/978-1-4614-7636-8_11,

The CMV Controversy

Cytomegalovirus (CMV) has always been one of the most frequently identified pathogens in solid organ transplantation, despite multiple prevention strategies that have been developed over time. Lung transplant recipients, among all other solid organ transplant recipients, appear to be particularly susceptible to CMV disease, recurrences, and antiviral resistance. In the early era of lung transplantation, prior to widespread use of ganciclovir-based prophylaxis, symptomatic CMV disease including CMV pneumonitis was very common, occurring in up to 60–80 % of patients [1]. The highest-risk group was identified as the donor-seropositive, recipient-seronegative (D+/R−) group, which corresponds to the introduction of CMV from the donor organ into a recipient without antecedent CMV immunity and, thus, limited ability (at least initially) to limit viral replication. In studies by Zeevi and others, the development of CMV-specific immunity was shown to be delayed in some D+/R− lung recipients, although most did develop such immunity eventually [2]. In most early studies, both CMV disease and donor CMV-seropositive serology were associated with worse outcomes, including increased risk of BOS, shorter time to BOS, and/or mortality [3–7]. In some studies, use of CMV prophylaxis was associated with decreased mortality [3] or delayed onset of BOS [1].

Mechanisms of CMV effects on the allograft are an area of active research. Studies in animal models (rat tracheal allografts) have supported the hypothesis of a causative role for CMV, in that obliterative bronchiolitis was accentuated by CMV and prevented by ganciclovir prophylaxis or hyperimmune serum [8]. In this model, CMV effects were accompanied by increases in interleukin-2 and tumor necrosis factor-alpha expression and a decrease in interleukin-10 expression [8]. Wiebe et al. found that both rat CMV and bacterial infection increased chronic airway rejection in a rat model, and this process was associated with increased expression of intercellular adhesion molecule (ICAM)-1 on endothelium, as well as increased numbers of infiltrating leukocytes and ED-1 positive macrophages [9].

More recently, CMV has been associated with increased activity of pro-inflammatory chemokines such as CXCL 10 [10, 11]. Increases in CXCL 10 (IP 10) in CMV-positive BAL samples were associated with a decrease in FEV1 in a study by Weseslindtner et al. [10]. Weigt et al. found that pulmonary CMV was associated with increased levels of the chemokines CCL 2 and CCL 5, with CCL 2 being predictive of BOS development and CCL 5 predictive of mortality [12]. In addition, the role of recipient genetic polymorphisms in determining CMV risk has generated increasing interest [11], including a polymorphism affecting interferon-gamma levels [13]. Recent work has suggested that CMV levels in epithelial lining fluid are more relevant that those in plasma [14].

Studies that have assessed the putative association of CMV with BOS or allograft dysfunction are summarized in Table 11.1. Recently, the impact of treated CMV pneumonitis in the prophylaxis era has been reassessed, with studies showing disparate results: both a decreased impact [15] and a continued adverse impact [16, 17] of CMV pneumonitis on allograft function have been reported. Tamm et al.

Table 11.1 Studies of the association between CMV infection, disease, or serostatus and the risk of developing bronchiolitis obliterans syndrome and allograft dysfunction

Year	Author	References	No. of patients	Main findings
1991	Keenan et al.	[7]	27	CMV serology and CMV infection: increased risk for BOS
1992	Cerrina et al.	[5]	36	CMV D+/R−, CMV pneumonitis, and CMV recurrence: increased risk for BOS
1995	Bando et al.	[3]	239	CMV D+/R−: risk for BOS and death; survival improved with prophylaxis
1996	Girgis et al.	[49]	74	CMV added additional risk to the acute rejection score for BOS risk
1996	Soghikian et al.	[1]	89	CMV prophylaxis with ganciclovir delays BOS onset
1996	Sharples et al.	[88]	157	CMV infection and CMV disease: increased risk for BOS
1997	Kroshus et al.	[4]	132	CMV pneumonitis: increased risk for BOS and time to BOS
1998	Gutierrez et al.	[89]	61	On prophylaxis, donor serology but not CMV infection or CMV disease predicts BOS
1998	Heng et al.	[6]	230	CMV serology and CMV disease: increased risk for BOS
1998	Smith et al.	[90]	301	CMV D+/R−: increased risk for BOS within 3 years
1999	Speich et al.	[91]	22	Oral ganciclovir prophylaxis, decreased risk for BOS
2001	Schulman et al.	[92]	152	CMV pneumonitis: increased risk for BOS
2002	Fiser et al.	[93]	134	CMV infection: increased risk for BOS progression
2002	Jackson et al.	[94]	204	CMV not associated with acute-onset BOS
2003	Luckraz et al.	[95]	297	BOS in CMV D−/R− not significantly different from D+ and/or R+
2003	Westall et al.	[96]	26	Early CMV DNAemia associated with BOS risk despite prophylaxis
2004	Tamm et al.	[15]	341	Treated CMV pneumonitis and CMV serology: not risk factors for BOS
2005	Hachem et al.	[97]	157	ATG decreases BOS risk vs. basiliximab, but no difference in CMV
2005	Perreas et al.	[98]	146	CMV prophylaxis (3 months.) decreased CMV but not BOS risk
2006	Moffatt-Bruce et al.	[99]	128	Heart-lung recipients had more CMV than lung patients but BOS same
2006	Ruttmann et al.	[100]	68	CMV Ig addition to ganciclovir decreased CMV disease and BOS at 3 years
2008	Chmiel et al.	[101]	96	CMV prophylaxis decreased BOS and increased survival at 5 years
2008	Kwakkel-van Erp et al.	[102]	48	Lack of activating KIR correlates with BOS but not CMV
2008	Solidoro et al.	[103]	46	No difference in OB with combined prophylaxis

(continued)

Table 11.1 (continued)

Year	Author	References	No. of patients	Main findings
2008	Valentine et al.	[18]	151	CMV pneumonitis in 38 % of patients who stopped prophylaxis; 50 % of these developed BOS in 1 year
2008	Weigt et al.	[12]	72	CCL 2 and CCL 5 in CMV pneumonitis; CCL 2 predicted BOS risk and CCL 5 predicted mortality
2009	Manuel et al.	[35]	93	CMV detection in BAL is not associated with increased BOS risk
2009	Ranganathan et al.	[104]	599	CMVIg prophylaxis not related to BOS risk in pediatric lung recipients
2009	Valentine et al.	[17]	161	CMV pneumonitis in first 100 days increased BOS risk
2010	Snyder et al.	[16]	231	Treated CMV pneumonitis remains a risk for BOS and death
2011	Paraskeva et al.	[105]	192	CMV detection in BAL is associated with increased BOS risk
2011	Kwakkel-van Erp et al.	[106]	85	Mannose-binding-lectin deficiency increased CMV reactivation but no effect on BOS

ATG antithymocyte globulin, *CMV* cytomegalovirus, *CMV Ig* CMV hyperimmune globulin, *CMV D+/R−* CMV donor seropositive, recipient seronegative, *CMV R+* recipient seropositive, *CMV D−/R−* CMV donor seronegative, recipient seronegative, *KIR* killer immunoglobulin-like receptor, *OB* obliterative bronchiolitis

studied 341 lung recipients, including 151 with CMV pneumonia who were treated with ganciclovir, and 190 without CMV pneumonia. There were no significant differences in BOS or in patient survival at 1, 3, and 5 years [15]. There was also no association between CMV donor/recipient serostatus and BOS or survival [15]. Snyder et al., however, reported that there was an association between treated CMV pneumonitis and BOS. [16]. In 231 patients transplanted between 2000 and 2004, 1,887 biopsies were performed including CMV immunostaining. CMV pneumonitis developed in 49 (21 %). Treated CMV pneumonitis within the first 6 months increased the risk of BOS (hazard ratio 2.19) and death (hazard ratio 1.89). This remained significant in multivariable analysis [16]. Similarly, Valentine et al. assessed the impact of respiratory infections due to a variety of pathogens and found that CMV pneumonitis in the first 100 days increased BOS risk with a hazard ratio of 3.1 [17]. In another study, Valentine et al. reported that indefinite ganciclovir prophylaxis was associated with long-term freedom from CMV pneumonitis, but that in the group of patients who stopped prophylaxis, 38 % developed CMV pneumonitis, and 50 % of these developed BOS within 1 year [18].

Thus, some controversy still exists, but most evidence suggests at least some role for CMV. In the current era, several important differences have emerged as compared with the earlier era. CMV pneumonitis has notably declined, comprising, for example, only 4.3 % of a set of 559 respiratory infections in lung recipients in a

Table 11.2 Organisms that have been associated with risk of developing bronchiolitis obliterans syndrome and allograft dysfunction

Viral
Cytomegalovirus
Other herpesviruses: human herpesvirus-6, human herpesvirus-7, Epstein-Barr virus
Community respiratory viruses: influenza, parainfluenza, respiratory syncytial virus, adenovirus, metapneumovirus, rhinovirus, coronavirus, others
Bacterial
Pseudomonas aeruginosa
Other gram-negative bacteria (*Burkholderia* spp., *Klebsiella* spp., others)
Gram-positive bacteria (*Staphylococcus* spp., *Streptococcus* spp., others)
Chlamydophila (Chlamydia) *pneumoniae*
Mycobacteria
Simkania negevensis
Fungal
Aspergillus spp.
Pneumocystis jiroveci (formerly *P. carinii*)

study by Valentine et al. [19]. Longer-term viral suppression has become an option because of the availability of oral valganciclovir. In a randomized, multicenter study, CMV events and severity were significantly decreased in the group receiving 12 months as compared with 3 months of valganciclovir prophylaxis [20]. This benefit was maintained out to >4 years in a single-center subgroup [21]. Whether this enhanced freedom from CMV events improves the lifespan of the allograft is still a question. As mentioned above, the study by Valentine et al. of increased CMV pneumonitis and BOS in the group that stopped prophylaxis has led this group to call for indefinite long-term prophylaxis [18].

In addition, methods of CMV detection have become increasingly sophisticated, especially with the development of quantitative measures of blood and BAL viral loads, allowing for detection of early and/or subclinical infection [14, 22–25], with particular recent attention to the lung compartment over blood or plasma [14, 25]. There has also been increasing recognition in other solid organ transplant recipients of the importance of subclinical CMV infection on allograft function (e.g., cardiac allograft vasculopathy in heart recipients) [26, 27]. Whether such early detection, particularly of late CMV after cessation of prophylaxis, improves allograft function for lung recipients also remains to be shown. Given the results of Bauer et al. regarding CMV detection in epithelial lining fluid, it has been questioned whether monitoring of viremia is adequate for early detection [14]. Disparities in results between groups in the current era may also reflect more subtle differences. For example, the role of mixed infection with more than one CMV genotype is an area of active research [28].

Although CMV has received the most attention, multiple other organisms have been described as possible triggers for BOS. These include viral, bacterial, and fungal organisms (Table 11.2).

Other Herpesviruses

The herpesvirus family includes herpes simplex virus 1 and 2, varicella-zoster virus, CMV, Epstein-Barr virus (EBV), human herpesvirus 6 and 7 (HHV-6 and HHV-7), and human herpesvirus-8 (Kaposi's sarcoma herpesvirus). Of these, HHV-6 and 7, along with CMV, are termed the beta-herpesviruses. HHV-6 and 7 are the viruses that cause roseola in infants and can reactivate post-transplant, often in an earlier timeframe than CMV. HHV-6 reactivation, in particular, has been described to cause clinical syndromes that have some similarity to CMV, including pneumonitis, hepatitis, meningoencephalitis, and pancytopenia. [29] HHV-6 pneumonitis was identified as one of the causes of apparent culture-negative interstitial pneumonitis in bone marrow transplant recipients [30].

Of the herpesviruses listed above, HHV-6, HHV-7, and EBV have been reported in association with BOS or similar syndromes. Neurohr et al. performed a panel of viral PCR tests on BAL fluid from 87 lung recipients and found that HHV-6, which was detected in 20 patients, was an independent risk factor for BOS and death [31]. On the other hand, Ross et al. found a possible association between HHV-7 detection and bronchiolitis obliterans with organizing pneumonia after lung transplantation [32]. The possible role of EBV was studied by Engelmann et al., who monitored 385 lung transplant recipients for CMV (by pp65 antigenemia assay), EBV DNA, and adenovirus DNA in blood [33]. Over half of the patients had EBV DNA detected on at least one occasion, and repeated EBV DNA detection was associated with BOS risk [33]. Diagnosis of BOS prior to study entry, retransplantation, and the use of sirolimus or everolimus were associated with detection of EBV [33]. This latter finding was somewhat surprising, as the sirolimus group of immunosuppressive agents has been thought to have a protective effect with respect to viral infections as compared with other immunosuppressive agents [34].

In contrast to the above studies, a recent study by Manuel et al. of viral PCR detection in BAL did not show an association between CMV, HHV-6, or HHV-7, on the one hand, and BOS or acute rejection, on the other, although half of the patients had CMV detected and one-fifth each had HHV-6 and HHV-7 detected [35]. Differences in baseline patient populations, immunosuppression, prophylaxis, and detection methods might account for some of the differences in findings, but these remain largely unexplained. Manuel et al. hypothesized that prolonged antiviral prophylaxis, while not preventing viral reactivation within the allograft, might mitigate some of its damaging effects [35]. Although reports of associations of BOS with detection of these other herpesviruses are intriguing, the disparate results from different centers must introduce a note of caution when assessing the impact of these viruses overall.

Community Respiratory Viruses

Lung transplant recipients are highly susceptible to infection by community-acquired respiratory viruses (CARVs), particularly at times of intensified immunosuppression. Such infection may be asymptomatic or may involve the upper or lower respiratory tract. Occasionally infectious syndromes can be severe enough to warrant ICU admission and mechanical ventilation. In addition to such dramatically symptomatic episodes, however, less symptomatic but truly chronic infections have also been documented, even with the comparatively underrated and ubiquitous rhinovirus [36]. The major question with regard to CARVs (in addition to the direct infectious syndromes they produce) is the indirect and longer-lasting effect on the allograft. Mechanisms are being investigated, and recent attention has focused on the increase in the chemokine receptor CXCR 3 and its chemokine ligands. Weigt et al. compared BAL fluid in CARV and non-CARV-infected lung recipients and found that elevated levels of CXCL 10 and CXCL 11 correlated with greater decreases in FEV1 when measured 6 months after the initial infection episode [37].

Multiple studies have demonstrated an impact of community respiratory viral infection on allograft function, not only during the acute infectious process but also 3 and 6 months after resolution, although results have varied. Kumar et al. studied 100 patients from 2001 to 2003, comparing 50 patients with clinically diagnosed viral respiratory infections and 50 who were asymptomatic [38]. Nasopharyngeal and throat swabs revealed viral pathogens in two-thirds of the group with clinical respiratory infection [including rhinovirus, coronavirus, respiratory syncytial virus (RSV), influenza, parainfluenza, and human metapneumovirus]. The incidence of acute rejection and of decline in FEV1 over 3 months was significantly higher in the viral respiratory infections group, and for some patients, the decline in FEV1 was sustained out to 1 year [38]. A more recent prospective study by this group utilized a multiplex panel of molecular detection assays for 19 viruses on BAL samples of 93 lung recipients. Eighty-one BAL samples were positive for viruses; rhinovirus was detected in 46, and smaller numbers of recipients had parainfluenza, coronavirus, influenza, metapneumovirus, or RSV. Acute rejection or $\geq$20 % decline in FEV1 over 3 months occurred in 33.3 % of virus-positive vs. 6.7 % of virus-negative patients ($p = 0.001$). This was true regardless of whether the viral infection was symptomatic or not [39]. In another study, Gottlieb et al. followed 388 lung recipients with nasopharyngeal and oropharyngeal viral swabs for 12 community respiratory viruses and found that 7.7 % of patients manifested a CARV infection. BOS occurred at 1 year in 25 % of CARV-positive patients vs. 9 % of CARV-negative patients ($p = 0.002$) [40]. RSV and parainfluenza virus appeared to have more of an effect than rhinovirus and coronavirus. Symptomatic CARV remained a risk factor for BOS in multivariable analyses but did not appear to influence progression of preexisting BOS [40]. Khalifah et al. followed 259 adult lung recipients and found that CARV infection was associated with BOS, death, and death from BOS [41]. In this study, these effects were particularly strong for lower-tract CARV infection [41]. In a study by Vilchez et al., parainfluenza virus was especially strongly associated with subsequent BOS (32 %) [42].

A few studies have not shown the same impact of CARVs. A study of pediatric lung recipients by Liu et al. found that over half developed CARV infections, but these infections were not associated with chronic allograft dysfunction or death in this particular cohort [43]. In another report of 576 pediatric lung recipients in a multicenter study by Liu et al., CARV infection was associated with decreased 12-month survival but not with acute rejection [44]. A study of 50 adult lung recipients by Milstone et al. found that one-third developed CARV infection, but this was not associated with subsequent graft dysfunction [45]. Soccal et al. performed both BAL and nasopharyngeal swabs and found that 29.3 % of the upper respiratory and 17.2 % of the BAL samples were virus-positive. Acute rejection was not associated with viral infection but recovery of lung function was significantly slower when both infection and rejection were present [46]. Finally, Vu et al. performed an analysis of 34 pooled studies and confirmed an association between respiratory viral infections and symptoms, but not BOS [47].

Thus, there are some studies that provide evidence in favor of an association of CARV infection with BOS, but this was not confirmed in an analysis of pooled studies. Further multicenter studies would be of interest, involving uniform monitoring assays and protocols. The potential effects of antiviral therapy on preservation of allograft function are discussed in the section on treatment below.

Bacterial Infections

Whereas CMV infections have decreased in frequency, bacterial infections remain a common post-transplant complication [48]. In a study by Valentine et al., over 80 % of lung pathogens in the current era were bacterial, and more than half of these were *Pseudomonas aeruginosa* [19]. While bacterial infections in general have been identified as a risk factor for BOS [6, 49], *Pseudomonas* has been of particular interest [50]. It has been noted since the early days of lung transplantation that infection and colonization with *Pseudomonas* spp., including multidrug-resistant strains, is extremely common in lung recipients [51, 52]. Whereas many CF and bronchiectasis patients are colonized with *Pseudomonas* pre-transplant, Pseudomonas may also be acquired de novo post-transplant in any recipient, and is associated with an intense inflammatory response [52]. In one study by Botha et al., de novo acquisition of *Pseudomonas* was associated with increased risk of BOS within 2 years (23.4 % vs. 7.7 %, $p=0.006$) [53]. *Pseudomonas* colonization preceded BOS by a median of 204 days [53]. Gottlieb et al. reported that *Pseudomonas* colonization post-transplant in CF patients was a risk for BOS, whereas eradication of previous *Pseudomonas* colonization was associated with less frequent BOS ($p=0.006$) [54]. In addition, a variety of both enteric (*E. coli, Klebsiella, Enterobacter, Proteus*, etc.) and non-enteric gram-negative organisms (*Stenotrophomonas, Alcaligenes, Acinetobacter*, etc.) may be isolated from post-transplant BAL cultures, particularly in those patients with airway complications and/or protracted post-transplant recovery and ventilator courses. *Burkholderia cepacia*

complex has been associated with high mortality post-transplant (particularly *B. cenocepacia* or genomovar III), although much of that mortality is due to direct infectious syndromes rather than long-term effects of colonization.

Gram-positive organisms, including methicillin-resistant *Staphylococcus aureus* (MRSA), have been increasingly identified as significant causes of post-transplant morbidity [55]. Gupta et al. reported that gram-positive infections occurred in 40 % of lung recipients, mostly *S. aureus* (of which 42 % was MRSA) [55]. MRSA can be acquired from the donor, can be related to pre-transplant colonization in the recipient, or can be acquired de novo post-transplant from sources other than the donor. In the study by Gupta et al., gram-positive lung infections were associated with risk of development of BOS and also with surgical airway complications [55]. Valentine et al. identified both gram-positive and gram-negative infections as associated with increased risk for BOS [17].

Mycobacterial infections, although less common than conventional bacterial infections, are also associated with morbidity and, in some settings, decreased survival after lung transplantation [56]. In the case of *Mycobacterium tuberculosis*, this morbidity is largely related to direct infectious syndromes, [57] whereas colonization with non-tuberculous mycobacteria can be associated with a spectrum of clinical manifestations, including asymptomatic colonization. Whether non-tuberculous mycobacterial infection predisposes to BOS is as yet uncertain, but in a study by Huang et al., non-tuberculous mycobacterial infection was associated with increased mortality independent of BOS [56].

Possible mechanisms of the allograft effects of bacterial colonization might include increased neutrophilic and other inflammatory responses [52] that lead to release of cytokines and chemokines; up-regulation of endothelin-1 [58]; or predisposition to other infections, including viral and fungal infections that might additionally increase risk for BOS. Borthwick et al. reported that *Pseudomonas* can serve as a cofactor in TGF-beta-1-driven epithelial-to-mesenchymal transition, which has been implicated in the pathogenesis of BOS [59]. The intriguing possible relationship of *Pseudomonas* colonization to gastroesophageal reflux has been explored by Vos et al. [60].

More subtle and difficult-to-culture organisms such as *Chlamydophila pneumoniae* (Chlamydia) have recently attracted interest [61], particularly as such organisms may be responsive to azithromycin. *Chlamydophila pneumoniae* is best detected by PCR from BAL fluid rather than culture. Such organisms have been studied in a variety of non-transplant settings because of their affinity for endothelium. Glanville et al. reported that *C. pneumoniae* was detected in BAL samples in 25 % of lung recipients and was associated with higher risk for early mortality, acute rejection, and BOS [61]. In another study by Kotsimbos et al. [62], Chlamydia D+/R− status was associated with a BOS incidence of 75 %; whereas low anti-*C. pneumoniae* titers in the donor and high anti-*C. pneumoniae* titers in the recipient were found to be predictive of freedom from BOS, suggesting that stronger antecedent recipient immunity to *C. pneumoniae* might be helpful in ameliorating effects of donor-derived *C. pneumoniae* in the allograft [62].

Husain et al. investigated the novel chlamydia-like organism, *Simkania negevensis*, in lung recipients [63]. This study found that detection of *S. negevensis* was frequent (40/41 recipients) and was associated with concomitant acute rejection [63]. The effects of *S. negevensis* on chronic allograft dysfunction are not yet known; however, because acute rejection is a risk factor for BOS, an association with acute rejection (if confirmed) might also mean an association with longer-term BOS risk.

Interestingly, *Clostridium difficile* colitis, although not an infection that affects the lung directly, was associated with increased risk of BOS in a study by Gunderson et al., particularly when *C. difficile* occurred in the early post-transplant period [64]. Whether early *C. difficile* is a marker for other complications that predispose to BOS or whether the inflammatory milieu induced by *C. difficile* infection itself is responsible needs further study.

Fungal Infections

Fungal infections, particularly aspergillosis, have long been identified as a source of morbidity and mortality in the lung transplant recipient [19, 49, 65]. Risk factors are described in the section on prevention below. Traditionally, fungal processes have been defined as invasive fungal infection or as colonization. The effects of fungal infection on the allograft have been less frequently studied than those of viral or bacterial infections. Valentine et al. identified fungal pneumonia as a significant risk factor for subsequent BOS [17]. Recent intriguing evidence from Weigt et al. has demonstrated that aspergillus colonization, even in the absence of invasive infection, is a risk factor for BOS and BOS-related mortality, independent of acute rejection [66]. Aspergillus colonization preceded BOS by a median of 261 days in this study [66]. However, neither fungal colonization nor pulmonary fungal infection was identified as a risk factor for chronic allograft dysfunction in a study of 55 pediatric lung recipients by Liu et al. [67], although pulmonary fungal infection was associated with greater 12-month mortality in a large multicenter pediatric cohort [68]. It would be of interest to determine whether there are differential effects of different antifungal prophylaxis strategies. The changing landscape of antifungal prophylaxis, particularly the shift towards voriconazole and away from itraconazole, is of interest [69, 70]. Although antifungal prophylaxis has traditionally been undertaken with a goal of preventing invasive fungal infection, perhaps the results of Weigt et al. (described above) will prompt reassessment of current antifungal prophylaxis strategies with an eye to decreasing colonization as well. In particular, it could be asked if the addition or substitution of inhaled amphotericin or liposomal amphotericin preparations [71, 72] might lead to decreased airway fungal colonization compared with systemic-only antifungal strategies, and long-term benefits to the allograft should be further explored.

Prevention of Infection-Associated BOS and Allograft Dysfunction

The following section assumes that infections do predispose to BOS, although in the case of each group of organisms, the evidence, including dissenting evidence, is reviewed above. If CMV does pose a significant risk for BOS development, an important question is whether the key risk factor is symptomatic CMV disease, subclinical viremia, or subclinical replication in the lung compartment [14]. As discussed above and summarized in Table 11.1, some but not all studies have suggested a beneficial effect of CMV prophylaxis on decreasing BOS risk. A variety of prevention strategies are effective in preventing symptomatic CMV disease, but prevention of subclinical viremia likely requires longer prophylaxis or preemptive therapy (or both), since asymptomatic viremia might otherwise occur without detection. As mentioned above, Valentine et al. called for indefinite prophylaxis, related to the finding that the group that stopped prophylaxis had high rates of CMV pneumonitis and progression to BOS within 1 year [18]. From the randomized, controlled trial by Palmer et al., it is known that CMV outcomes are significantly decreased with a 12-month course of valganciclovir prophylaxis compared with a 3-month course, but whether that benefit translates into improved long-term results for the allograft needs to be investigated further.

CMV prophylaxis might also work by decreasing replication of other herpesviruses such as EBV and HHV-6, but since the impact of those viruses on the allograft is controversial (see above), it cannot yet be concluded that this mechanism is contributory.

Other methods of CMV prevention include avoidance of CMV exposures for D−/R− patients (including use of CMV-free blood if any blood transfusions are needed), and the development of CMV vaccines in the future. If the highest-risk group (D+/R−) can be transformed into D+/R+ by pre-transplant vaccination, the risk of CMV might be ameliorated significantly in this group. Recent studies of a glycoprotein B CMV vaccine are promising in pre-transplant patients [73].

Regarding community respiratory viruses, the most important methods of prevention are immunization (for influenza) and rigorous infection control. Influenza immunization has been shown to be safe in transplant recipients, as larger studies have not corroborated any clinically significant increase in rejection or allograft dysfunction in solid organ transplant recipients [74]. The efficacy of influenza vaccine may be suboptimal, particularly in those recipients with recent transplants or intensified immunosuppression, but per current guidelines [74], partial protection is preferable to no immunization. It is also extremely important that family members and health care workers be immunized, to decrease risk of transmission of influenza to the patient. If the transplant recipient does acquire influenza despite these measures, early detection and antiviral treatment can reduce morbidity, including the need for ICU admission [75]. It is important to get this message out to primary care providers, urgent care, and emergency room clinicians, who may (rather than the transplant team) be the first to assess a transplant recipient with a viral illness.

Each year the types of circulating influenza strains and the patterns of antiviral resistance are different; clinicians should follow yearly updates from their national health organizations with each year's recommendations for antiviral therapy.

For any respiratory virus, stringent hospital infection control is essential. Outbreaks of respiratory infection, including RSV and parainfluenza, can be devastating to transplant wards. Early viral detection with nasopharyngeal swabs (even in minimally symptomatic patients) is important in limiting in-hospital transmission. Adherence to recommended precautions and to hand hygiene is essential, and programs that increase compliance with these measures will have a beneficial effect for all patients, including vulnerable transplant recipients. Health care workers with respiratory viral illnesses should ideally not have contact with transplant recipients at all, but if such contact is unavoidable, all possible measures should be taken to prevent transmission (including mask, gloves, limiting time in room, etc.). Transplant centers should develop policies that do not penalize employees for absenteeism due to illness. Educational efforts should emphasize that mild viral symptoms in a health care worker (that a worker might tend to ignore or to "work through") can translate into acute respiratory failure and/or long-term loss of allograft function in a lung recipient. Educating patients and family members regarding avoidance of out-of-hospital exposures, as well as the importance of early reporting of symptoms, are also important measures.

The role of antiviral therapy for non-influenza respiratory viruses is still evolving. Many centers use ribavirin preparations for treatment of symptomatic RSV infection [76] and sometimes parainfluenza virus [77] and metapneumovirus infection as well [78], although further data would be welcome. Most literature to date has reported on aerosolized ribavirin, but inconvenience and potential toxicity to health care workers has led to the study of other ribavirin preparations. Glanville et al. described the use of intravenous ribavirin plus oral corticosteroids in 18 lung recipients, in whom an initial fall in FEV1 was followed by recovery at 3 months, and only one patient developed subsequent BOS [79]. Intravenous ribavirin is not currently available in the United States. Similarly, promising preliminary results from a study by Pelaez et al. demonstrated preservation of allograft function in a group of lung recipients with RSV who received a regimen of 10 days of oral ribavirin in combination with high-dose steroids for the first 3 days [80]. In addition, Fuehner et al. reported on a nonrandomized study of 38 patients who received oral ribavirin compared with 29 who did not, during paramyxovirus infection. Whereas both groups had declines in FEV1, a greater percentage of ribavirin-treated patients recovered lung function within 1 month (84 % vs. 59 %, $p=0.02$). New-onset BOS within 6 months occurred in 5 % of the ribavirin vs. 24 % of the non-ribavirin-treated patients [77]. Novel therapies are also under development. A recent study of a small interfering RNA (siRNA) treatment for RSV infection demonstrated a decrease in new-onset BOS and progression to BOS by day 90 in the treatment group ($n=16$), as compared with others ($n=8$) who received standard care for RSV infection (6.3 % vs. 50 %, $p=0.027$) [81]. The likely availability of other antiviral therapies in the future would make larger, multicenter comparative effectiveness trials that include long enough follow up to detect effects on time to BOS desirable.

Prevention of bacterial infections is also a matter of infection control and hand hygiene. Immunizations for *Pneumococcus* and for pertussis (in the form of Tdap vaccine for adults) should be kept up to date and ideally should be updated during the pre-transplant evaluation phase [82]. Given the results of Gottlieb et al. regarding decreased risk in patients in whom prior *Pseudomonas* colonization was eradicated, strategies that enhance eradication are likely to produce long-term benefit for the allograft [54]. Such strategies might include individualized peri-transplant combinations of systemic and inhaled antibiotics, as well as pre-transplant attention to potential reservoirs such as the sinuses. If effective vaccines for prevention of *Pseudomonas* infection and colonization become available in the future, that would be an important intervention. The effects of airway interventions such as stents should also be considered, as foreign bodies in the airway can serve as a nidus for bacterial colonization, albeit an important intervention in prevention of post-obstructive pneumonia and allograft dysfunction.

The demonstrated effects of azithromycin in protecting the allograft from BOS [83, 84] do bring up the question as to whether prevention of infection, including subclinical infection with organisms that lack a cell wall (e.g., *Chlamydophila, Mycoplasma, Simkania*) might be one of the mechanisms that contribute to such protection. More work in this area would be of interest. The risk of emergence of azithromycin resistance in these organisms is also worthy of future study.

Prevention of fungal infections is informed by an understanding of risk factors. Exposures related to the external environment should be minimized, including protection from the effects of hospital construction. Transplant recipients should be educated about the risks of marijuana smoking, gardening, farming, construction work, composting, cave exploration, and other activities that they consider undertaking as they recover from the initial post-transplant phase and begin to resume a more normal life [85]. Antifungal prophylaxis is now utilized by many lung transplant programs, most frequently using azole antifungal agents, inhaled amphotericin preparations, combinations of the above, and sometimes other agents [69, 70]. Regarding the type of azole used, there has been a shift from itraconazole towards voriconazole over time [70]. However, even in the presence of antifungal prophylaxis, breakthrough fungal infections may occur. In fact, antifungal prophylaxis may select out for certain types of fungal organisms (e.g., zygomycetes in the setting of voriconazole prophylaxis.) Protocol BALs can help with detection of fungal colonization in the asymptomatic patient and might prompt either a change of prophylaxis or increased clinical and radiographic monitoring or both. The occurrence of fungal infections late in the post-transplant course (after discontinuation of prophylaxis) might be related to late rejection, environmental exposures, or a reservoir in the native lung for single-lung transplant recipients. An enhanced clinical awareness in patients falling into any of the above groups is helpful.

For prevention of *Pneumocystis jiroveci* pneumonia (PJP, formerly *P. carinii*), center-specific practices have varied, but some clinicians (e.g., Gordon et al.) have recommended to continue PJP prophylaxis long-term (lifelong) in lung recipients, as they, uniquely among solid organ recipients, continue to have significant PJP risk beyond the first year [86]. Trimethoprim-sulfamethoxazole is the most commonly

used agent and has the added benefit of preventing several other infections (toxoplasmosis, listeriosis). For sulfa-allergic or intolerant patients, monthly aerosolized pentamidine, oral dapsone, or oral atovaquone are alternative prophylaxis options.

Whereas many previous studies have focused on individual infectious agents, the overall microbial ecology (the microbiome) of the allograft may be a more fruitful area of study [87]. Immune responses to different infectious agents may be intertwined, and ideally in the future, interventions should be assessed in terms of alteration of the microbiome rather than just impact on one particular organism.

Conclusion

A growing body of literature has linked the risk for new-onset or progressive BOS to a variety of infections, including CMV, other herpesviruses, CARVs, and bacterial and fungal infections. Although results from different centers have varied, it appears that infections play a role in BOS development in at least some settings, and mechanistic considerations (e.g., chemokines) and animal models support this hypothesis. Recent studies support longer durations of CMV prophylaxis. The role of colonization as opposed to active infection (in the case of bacteria or fungi) and the role of subclinical viral infection in the allograft are areas of considerable interest. To the extent that infections trigger BOS, development of newer strategies (including vaccines and immunotherapies) that enable early detection and intervention will be important in providing long-term preservation of allograft function.

References

1. Soghikian MV, Valentine VG, Berry GJ, Patel HR, Robbins RC, Theodore J. Impact of ganciclovir prophylaxis on heart-lung and lung transplant recipients. J Heart Lung Transplant. 1996;15(9):881–7.
2. Zeevi A, Morel P, Spichty K, Dauber J, Yousem S, Williams P, et al. Clinical significance of CMV-specific T helper responses in lung transplant recipients. Hum Immunol. 1998;59(12):768–75.
3. Bando K, Paradis IL, Komatsu K, Konishi H, Matsushima M, Keena RJ, et al. Analysis of time-dependent risks for infection, rejection, and death after pulmonary transplantation. J Thorac Cardiovasc Surg. 1995;109(1):49–57; discussion 57–9.
4. Kroshus TJ, Kshettry VR, Savik K, John R, Hertz MI, Bolman 3rd RM. Risk factors for the development of bronchiolitis obliterans syndrome after lung transplantation. J Thorac Cardiovasc Surg. 1997;114(2):195–202.
5. Cerrina J, Le Roy LF, Herve PH, Parquin F, Harari S, Chapelier A, et al. Role of CMV pneumonia in the development of obliterative bronchiolitis in heart-lung and double-lung transplant recipients. Transpl Int. 1992;5 Suppl 1:S242–5.
6. Heng D, Sharples LD, McNeil K, Stewart S, Wreghitt T, Wallwork J. Bronchiolitis obliterans syndrome: incidence, natural history, prognosis, and risk factors. J Heart Lung Transplant. 1998;17(12):1255–63.

7. Keenan RJ, Lega ME, Dummer JS, Paradis IL, Dauber JH, Rabinowich H, et al. Cytomegalovirus serologic status and postoperative infection correlated with risk of developing chronic rejection after pulmonary transplantation. Transplantation. 1991;51(2):433–8.
8. Tikkanen JM, Kallio EA, Bruggeman CA, Koskinen PK, Lemstrom KB. Prevention of cytomegalovirus infection-enhanced experimental obliterative bronchiolitis by antiviral prophylaxis or immunosuppression in rat tracheal allografts. Am J Respir Crit Care Med. 2001;164(4):672–9.
9. Wiebe K, Fraund S, Steinmuller C, Steinhoff G. Rat cytomegalovirus and Listeria monocytogenes infection enhance chronic rejection after allogenic rat lung transplantation. Transpl Int. 2005;18(10):1166–74.
10. Weseslindtner L, Nachbagauer R, Kundi M, Jaksch P, Kerschner H, Simon B, et al. Human cytomegalovirus infection in lung transplant recipients triggers a CXCL-10 response. Am J Transplant. 2011;11(3):542–52.
11. Uhlin M, Mattsson J, Maeurer M. Update on viral infections in lung transplantation. Curr Opin Pulm Med. 2012;18(3):264–70.
12. Weigt SS, Elashoff RM, Keane MP, Strieter RM, Gomperts BN, Xue YY, et al. Altered levels of CC chemokines during pulmonary CMV predict BOS and mortality post-lung transplantation. Am J Transplant. 2008;8(7):1512–22.
13. Mitsani D, Nguyen MH, Girnita DM, Spichty K, Kwak EJ, Silveira FP, et al. A polymorphism linked to elevated levels of interferon-gamma is associated with an increased risk of cytomegalovirus disease among Caucasian lung transplant recipients at a single center. J Heart Lung Transplant. 2011;30(5):523–9.
14. Bauer CC, Jaksch P, Aberle SW, Haber H, Lang G, Klepetko W, et al. Relationship between cytomegalovirus DNA load in epithelial lining fluid and plasma of lung transplant recipients and analysis of coinfection with Epstein-Barr virus and human herpesvirus 6 in the lung compartment. J Clin Microbiol. 2007;45(2):324–8.
15. Tamm M, Aboyoun CL, Chhajed PN, Rainer S, Malouf MA, Glanville AR. Treated cytomegalovirus pneumonia is not associated with bronchiolitis obliterans syndrome. Am J Respir Crit Care Med. 2004;170(10):1120–3.
16. Snyder LD, Finlen-Copeland CA, Turbyfill WJ, Howell D, Willner DA, Palmer SM. Cytomegalovirus pneumonitis is a risk for bronchiolitis obliterans syndrome in lung transplantation. Am J Respir Crit Care Med. 2010;181(12):1391–6.
17. Valentine VG, Gupta MR, Walker Jr JE, Seoane L, Bonvillain RW, Lombard GA, et al. Effect of etiology and timing of respiratory tract infections on development of bronchiolitis obliterans syndrome. J Heart Lung Transplant. 2009;28(2):163–9.
18. Valentine VG, Weill D, Gupta MR, Raper B, Laplace SG, Lombard GA, et al. Ganciclovir for cytomegalovirus: a call for indefinite prophylaxis in lung transplantation. J Heart Lung Transplant. 2008;27(8):875–81.
19. Valentine VG, Bonvillain RW, Gupta MR, Lombard GA, LaPlace SG, Dhillon GS, et al. Infections in lung allograft recipients: ganciclovir era. J Heart Lung Transplant. 2008;27(5):528–35.
20. Palmer SM, Limaye AP, Banks M, Gallup D, Chapman J, Lawrence EC, et al. Extended valganciclovir prophylaxis to prevent cytomegalovirus after lung transplantation: a randomized, controlled trial. Ann Intern Med. 2010;152(12):761–9.
21. Finlen Copeland CA, Davis WA, Snyder LD, Banks M, Avery R, Davis RD, et al. Long-term efficacy and safety of 12 months of valganciclovir prophylaxis compared with 3 months after lung transplantation: a single-center, long-term follow-up analysis from a randomized, controlled cytomegalovirus prevention trial. J Heart Lung Transplant. 2011;30(9):990–6.
22. Humar A, Michaels M. American Society of Transplantation recommendations for screening, monitoring and reporting of infectious complications in immunosuppression trials in recipients of organ transplantation. Am J Transplant. 2006;6(2):262–74.
23. Humar A, Snydman D. Cytomegalovirus in solid organ transplant recipients. Am J Transplant. 2009;9 Suppl 4:S78–86.

24. Kotton CN, Kumar D, Caliendo AM, Asberg A, Chou S, Snydman DR, et al. International consensus guidelines on the management of cytomegalovirus in solid organ transplantation. Transplantation. 2010;89(7):779–95.
25. Westall GP, Michaelides A, Williams TJ, Snell GI, Kotsimbos TC. Human cytomegalovirus load in plasma and bronchoalveolar lavage fluid: a longitudinal study of lung transplant recipients. J Infect Dis. 2004;190(6):1076–83.
26. Tu W, Potena L, Stepick-Biek P, Liu L, Dionis KY, Luikart H, et al. T-cell immunity to subclinical cytomegalovirus infection reduces cardiac allograft disease. Circulation. 2006;114(15):1608–15.
27. Potena L, Holweg CT, Vana ML, Bashyam L, Rajamani J, McCormick AL, et al. Frequent occult infection with cytomegalovirus in cardiac transplant recipients despite antiviral prophylaxis. J Clin Microbiol. 2007;45(6):1804–10.
28. Gorzer I, Kerschner H, Jaksch P, Bauer C, Seebacher G, Klepetko W, et al. Virus load dynamics of individual CMV-genotypes in lung transplant recipients with mixed-genotype infections. J Med Virol. 2008;80(8):1405–14.
29. Ljungman P, Singh N. Human herpesvirus-6 infection in solid organ and stem cell transplant recipients. J Clin Virol. 2006;37 Suppl 1:S87–91.
30. Cone RW, Hackman RC, Huang ML, Bowden RA, Meyers JD, Metcalf M, et al. Human herpesvirus 6 in lung tissue from patients with pneumonitis after bone marrow transplantation. N Engl J Med. 1993;329(3):156–61.
31. Neurohr C, Huppmann P, Leuchte H, Schwaiblmair M, Bittmann I, Jaeger G, et al. Human herpesvirus 6 in bronchalveolar lavage fluid after lung transplantation: a risk factor for bronchiolitis obliterans syndrome? Am J Transplant. 2005;5(12):2982–91.
32. Ross DJ, Chan RC, Kubak B, Ardehali A, Laks H, Nichols WS. Bronchiolitis obliterans with organizing pneumonia: possible association with human herpes virus-7 infection after lung transplantation. J Heart Lung Transplant. 2001;20(2):171.
33. Engelmann I, Welte T, Fuhner T, Simon AR, Mattner F, Hoy L, et al. Detection of Epstein-Barr virus DNA in peripheral blood is associated with the development of bronchiolitis obliterans syndrome after lung transplantation. J Clin Virol. 2009;45(1):47–53.
34. Krams SM, Martinez OM. Epstein-Barr virus, rapamycin, and host immune responses. Curr Opin Organ Transplant. 2008;13(6):563–8.
35. Manuel O, Kumar D, Moussa G, Chen MH, Pilewski J, McCurry KR, et al. Lack of association between beta-herpesvirus infection and bronchiolitis obliterans syndrome in lung transplant recipients in the era of antiviral prophylaxis. Transplantation. 2009;87(5):719–25.
36. Kaiser L, Aubert JD, Pache JC, Deffernez C, Rochat T, Garbino J, et al. Chronic rhinoviral infection in lung transplant recipients. Am J Respir Crit Care Med. 2006;174(12):1392–9.
37. Weigt SS, Derhovanessian A, Liao E, Hu S, Gregson AL, Kubak BM, et al. CXCR3 chemokine ligands during respiratory viral infections predict lung allograft dysfunction. Am J Transplant. 2012;12(2):477–84.
38. Kumar D, Erdman D, Keshavjee S, Peret T, Tellier R, Hadjiliadis D, et al. Clinical impact of community-acquired respiratory viruses on bronchiolitis obliterans after lung transplant. Am J Transplant. 2005;5(8):2031–6.
39. Kumar D, Husain S, Chen MH, Moussa G, Himsworth D, Manuel O, et al. A prospective molecular surveillance study evaluating the clinical impact of community-acquired respiratory viruses in lung transplant recipients. Transplantation. 2010;89(8):1028–33.
40. Gottlieb J, Schulz TF, Welte T, Fuehner T, Dierich M, Simon AR, et al. Community-acquired respiratory viral infections in lung transplant recipients: a single season cohort study. Transplantation. 2009;87(10):1530–7.
41. Khalifah AP, Hachem RR, Chakinala MM, Schechtman KB, Patterson GA, Schuster DP, et al. Respiratory viral infections are a distinct risk for bronchiolitis obliterans syndrome and death. Am J Respir Crit Care Med. 2004;170(2):181–7.
42. Vilchez RA, Dauber J, McCurry K, Iacono A, Kusne S. Parainfluenza virus infection in adult lung transplant recipients: an emergent clinical syndrome with implications on allograft function. Am J Transplant. 2003;3(2):116–20.

43. Liu M, Mallory GB, Schecter MG, Worley S, Arrigain S, Robertson J, et al. Long-term impact of respiratory viral infection after pediatric lung transplantation. Pediatr Transplant. 2010;14(3):431–6.
44. Liu M, Worley S, Arrigain S, Aurora P, Ballmann M, Boyer D, et al. Respiratory viral infections within one year after pediatric lung transplant. Transpl Infect Dis. 2009;11(4):304–12.
45. Milstone AP, Brumble LM, Barnes J, Estes W, Loyd JE, Pierson 3rd RN, et al. A single-season prospective study of respiratory viral infections in lung transplant recipients. Eur Respir J. 2006;28(1):131–7.
46. Soccal PM, Aubert JD, Bridevaux PO, Garbino J, Thomas Y, Rochat T, et al. Upper and lower respiratory tract viral infections and acute graft rejection in lung transplant recipients. Clin Infect Dis. 2010;51(2):163–70.
47. Vu DL, Bridevaux PO, Aubert JD, Soccal PM, Kaiser L. Respiratory viruses in lung transplant recipients: a critical review and pooled analysis of clinical studies. Am J Transplant. 2011;11(5):1071–8.
48. Speich R, van der Bij W. Epidemiology and management of infections after lung transplantation. Clin Infect Dis. 2001;33 Suppl 1:S58–65.
49. Girgis RE, Tu I, Berry GJ, Reichenspurner H, Valentine VG, Conte JV, et al. Risk factors for the development of obliterative bronchiolitis after lung transplantation. J Heart Lung Transplant. 1996;15(12):1200–8.
50. Vos R, Vanaudenaerde BM, De Vleeschauwer SI, Van Raemdonck DE, Dupont LJ, Verleden GM. De novo or persistent pseudomonal airway colonization after lung transplantation: importance for bronchiolitis obliterans syndrome? Transplantation 2008;86(4):624–5; author reply 635–6.
51. Flume PA, Egan TM, Paradowski LJ, Detterbeck FC, Thompson JT, Yankaskas JR. Infectious complications of lung transplantation. Impact of cystic fibrosis. Am J Respir Crit Care Med. 1994;149(6):1601–7.
52. Nunley DR, Grgurich W, Iacono AT, Yousem S, Ohori NP, Keenan RJ, et al. Allograft colonization and infections with pseudomonas in cystic fibrosis lung transplant recipients. Chest. 1998;113(5):1235–43.
53. Botha P, Archer L, Anderson RL, Lordan J, Dark JH, Corris PA, et al. Pseudomonas aeruginosa colonization of the allograft after lung transplantation and the risk of bronchiolitis obliterans syndrome. Transplantation. 2008;85(5):771–4.
54. Gottlieb J, Mattner F, Weissbrodt H, Dierich M, Fuehner T, Strueber M, et al. Impact of graft colonization with gram-negative bacteria after lung transplantation on the development of bronchiolitis obliterans syndrome in recipients with cystic fibrosis. Respir Med. 2009;103(5):743–9.
55. Gupta MR, Valentine VG, Walker Jr JE, Lombard GA, LaPlace SG, Seoane L, et al. Clinical spectrum of gram-positive infections in lung transplantation. Transpl Infect Dis. 2009;11(5):424–31.
56. Huang HC, Weigt SS, Derhovanessian A, Palchevskiy V, Ardehali A, Saggar R, et al. Nontuberculous mycobacterium infection after lung transplantation is associated with increased mortality. J Heart Lung Transplant. 2011;30(7):790–8.
57. Singh N, Paterson DL. Mycobacterium tuberculosis infection in solid-organ transplant recipients: impact and implications for management. Clin Infect Dis. 1998;27(5):1266–77.
58. Charpin JM, Stern M, Lebrun G, Aubin P, Grenet D, Israel-Biet D. Increased endothelin-1 associated with bacterial infection in lung transplant recipients. Transplantation. 2001;71(12):1840–7.
59. Borthwick LA, Sunny SS, Oliphant V, Perry J, Brodlie M, Johnson GE, et al. Pseudomonas aeruginosa accentuates epithelial-to-mesenchymal transition in the airway. Eur Respir J. 2011;37(5):1237–47.
60. Vos R, Blondeau K, Vanaudenaerde BM, Mertens V, Van Raemdonck DE, Sifrim D, et al. Airway colonization and gastric aspiration after lung transplantation: do birds of a feather flock together? J Heart Lung Transplant. 2008;27(8):843–9.

61. Glanville AR, Gencay M, Tamm M, Chhajed P, Plit M, Hopkins P, et al. Chlamydia pneumoniae infection after lung transplantation. J Heart Lung Transplant. 2005;24(2):131–6.
62. Kotsimbos TC, Snell GI, Levvey B, Spelman DW, Fuller AJ, Wesselingh SL, et al. Chlamydia pneumoniae serology in donors and recipients and the risk of bronchiolitis obliterans syndrome after lung transplantation. Transplantation. 2005;79(3):269–75.
63. Husain S, Kahane S, Friedman MG, Paterson DL, Studer S, McCurry KR, et al. Simkania negevensis in bronchoalveolar lavage of lung transplant recipients: a possible association with acute rejection. Transplantation. 2007;83(2):138–43.
64. Gunderson CC, Gupta MR, Lopez F, Lombard GA, LaPlace SG, Taylor DE, et al. Clostridium difficile colitis in lung transplantation. Transpl Infect Dis. 2008;10(4):245–51.
65. Nunley DR, Ohori P, Grgurich WF, Iacono AT, Williams PA, Keenan RJ, et al. Pulmonary aspergillosis in cystic fibrosis lung transplant recipients. Chest. 1998;114(5):1321–9.
66. Weigt SS, Elashoff RM, Huang C, Ardehali A, Gregson AL, Kubak B, et al. Aspergillus colonization of the lung allograft is a risk factor for bronchiolitis obliterans syndrome. Am J Transplant. 2009;9(8):1903–11.
67. Liu M, Worley S, Mallory Jr GB, Arrigain S, Robertson J, Schecter MG, et al. Fungal infections in pediatric lung transplant recipients: colonization and invasive disease. J Heart Lung Transplant. 2009;28(11):1226–30.
68. Danziger-Isakov LA, Worley S, Arrigain S, Aurora P, Ballmann M, Boyer D, et al. Increased mortality after pulmonary fungal infection within the first year after pediatric lung transplantation. J Heart Lung Transplant. 2008;27(6):655–61.
69. Husain S, Zaldonis D, Kusne S, Kwak EJ, Paterson DL, McCurry KR. Variation in antifungal prophylaxis strategies in lung transplantation. Transpl Infect Dis. 2006;8(4):213–8.
70. Neoh CF, Snell GI, Kotsimbos T, Levvey B, Morrissey CO, Slavin MA, et al. Antifungal prophylaxis in lung transplantation—a world-wide survey. Am J Transplant. 2011;11(2): 361–6.
71. Drew RH, Dodds Ashley E, Benjamin Jr DK, Duane Davis R, Palmer SM, Perfect JR. Comparative safety of amphotericin B lipid complex and amphotericin B deoxycholate as aerosolized antifungal prophylaxis in lung-transplant recipients. Transplantation. 2004;77(2):232–7.
72. Husain S, Capitano B, Corcoran T, Studer SM, Crespo M, Johnson B, et al. Intrapulmonary disposition of amphotericin B after aerosolized delivery of amphotericin B lipid complex (Abelcet; ABLC) in lung transplant recipients. Transplantation. 2010;90(11):1215–9.
73. Griffiths PD, Stanton A, McCarrell E, Smith C, Osman M, Harber M, et al. Cytomegalovirus glycoprotein-B vaccine with MF59 adjuvant in transplant recipients: a phase 2 randomised placebo-controlled trial. Lancet. 2011;377(9773):1256–63.
74. Kumar D, Blumberg EA, Danziger-Isakov L, Kotton CN, Halasa NB, Ison MG, et al. Influenza vaccination in the organ transplant recipient: review and summary recommendations. Am J Transplant. 2011;11(10):2020–30.
75. Kumar D, Michaels MG, Morris MI, Green M, Avery RK, Liu C, et al. Outcomes from pandemic influenza A H1N1 infection in recipients of solid-organ transplants: a multicentre cohort study. Lancet Infect Dis. 2010;10(8):521–6.
76. Hynicka LM, Ensor CR. Prophylaxis and treatment of respiratory syncytial virus in adult immunocompromised patients. Ann Pharmacother. 2012;46(4):558–66.
77. Fuehner T, Dierich M, Duesberg C, DeWall C, Welte T, Haverich A, et al. Single-centre experience with oral ribavirin in lung transplant recipients with paramyxovirus infections. Antivir Ther. 2011;16(5):733–40.
78. Raza K, Ismailjee SB, Crespo M, Studer SM, Sanghavi S, Paterson DL, et al. Successful outcome of human metapneumovirus (hMPV) pneumonia in a lung transplant recipient treated with intravenous ribavirin. J Heart Lung Transplant. 2007;26(8):862–4.
79. Glanville AR, Scott AI, Morton JM, Aboyoun CL, Plit ML, Carter IW, et al. Intravenous ribavirin is a safe and cost-effective treatment for respiratory syncytial virus infection after lung transplantation. J Heart Lung Transplant. 2005;24(12):2114–9.

80. Pelaez A, Lyon GM, Force SD, Ramirez AM, Neujahr DC, Foster M, et al. Efficacy of oral ribavirin in lung transplant patients with respiratory syncytial virus lower respiratory tract infection. J Heart Lung Transplant. 2009;28(1):67–71.
81. Zamora MR, Budev M, Rolfe M, Gottlieb J, Humar A, Devincenzo J, et al. RNA interference therapy in lung transplant patients infected with respiratory syncytial virus. Am J Respir Crit Care Med. 2011;183(4):531–8.
82. Danzinger-Isakov L, Kumar D. Guidelines for vaccination of solid organ transplant candidates and recipients. Am J Transplant. 2009;9 Suppl 4:S258–62.
83. Jain R, Hachem RR, Morrell MR, Trulock EP, Chakinala MM, Yusen RD, et al. Azithromycin is associated with increased survival in lung transplant recipients with bronchiolitis obliterans syndrome. J Heart Lung Transplant. 2010;29(5):531–7.
84. Vos R, Vanaudenaerde BM, Verleden SE, Van Raemdonck DE, Dupont LJ, Verleden GM. Azithromycin in posttransplant bronchiolitis obliterans syndrome. Chest 2011;139(5):1246; author reply 1247.
85. Avery RK, Michaels MG. Strategies for safe living following solid organ transplantation. Am J Transplant. 2009;9 Suppl 4:S252–7.
86. Gordon SM, LaRosa SP, Kalmadi S, Arroliga AC, Avery RK, Truesdell-LaRosa L, et al. Should prophylaxis for Pneumocystis carinii pneumonia in solid organ transplant recipients ever be discontinued? Clin Infect Dis. 1999;28(2):240–6.
87. Nakajima T, Palchevsky V, Perkins DL, Belperio JA, Finn PW. Lung transplantation: infection, inflammation, and the microbiome. Semin Immunopathol. 2011;33(2):135–56.
88. Sharples LD, Tamm M, McNeil K, Higenbottam TW, Stewart S, Wallwork J. Development of bronchiolitis obliterans syndrome in recipients of heart-lung transplantation—early risk factors. Transplantation. 1996;61(4):560–6.
89. Gutierrez CA, Chaparro C, Krajden M, Winton T, Kesten S. Cytomegalovirus viremia in lung transplant recipients receiving ganciclovir and immune globulin. Chest. 1998;113(4): 924–32.
90. Smith MA, Sundaresan S, Mohanakumar T, Trulock EP, Lynch JP, Phelan DL, et al. Effect of development of antibodies to HLA and cytomegalovirus mismatch on lung transplantation survival and development of bronchiolitis obliterans syndrome. J Thorac Cardiovasc Surg. 1998;116(5):812–20.
91. Speich R, Thurnheer R, Gaspert A, Weder W, Boehler A. Efficacy and cost effectiveness of oral ganciclovir in the prevention of cytomegalovirus disease after lung transplantation. Transplantation. 1999;67(2):315–20.
92. Schulman LL, Weinberg AD, McGregor CC, Suciu-Foca NM, Itescu S. Influence of donor and recipient HLA locus mismatching on development of obliterative bronchiolitis after lung transplantation. Am J Respir Crit Care Med. 2001;163(2):437–42.
93. Fiser SM, Tribble CG, Long SM, Kaza AK, Kern JA, Jones DR, et al. Ischemia-reperfusion injury after lung transplantation increases risk of late bronchiolitis obliterans syndrome. Ann Thorac Surg 2002;73(4):1041–7; discussion 1047–8.
94. Jackson CH, Sharples LD, McNeil K, Stewart S, Wallwork J. Acute and chronic onset of bronchiolitis obliterans syndrome (BOS): are they different entities? J Heart Lung Transplant. 2002;21(6):658–66.
95. Luckraz H, Sharples L, McNeil K, Wreghitt T, Wallwork J. Cytomegalovirus antibody status of donor/recipient does not influence the incidence of bronchiolitis obliterans syndrome in lung transplantation. J Heart Lung Transplant. 2003;22(3):287–91.
96. Westall GP, Michaelides A, Williams TJ, Snell GI, Kotsimbos TC. Bronchiolitis obliterans syndrome and early human cytomegalovirus DNAaemia dynamics after lung transplantation. Transplantation. 2003;75(12):2064–8.
97. Hachem RR, Chakinala MM, Yusen RD, Lynch JP, Aloush AA, Patterson GA, et al. A comparison of basiliximab and anti-thymocyte globulin as induction agents after lung transplantation. J Heart Lung Transplant. 2005;24(9):1320–6.
98. Perreas KG, McNeil K, Charman S, Sharples LD, Wreghitt T, Wallwork J. Extended ganciclovir prophylaxis in lung transplantation. J Heart Lung Transplant. 2005;24(5):583–7.

99. Moffatt-Bruce SD, Karamichalis J, Robbins RC, Whyte RI, Theodore J, Reitz BA. Are heart-lung transplant recipients protected from developing bronchiolitis obliterans syndrome? Ann Thorac Surg 2006;81(1):286–91; discussion 291.
100. Ruttmann E, Geltner C, Bucher B, Ulmer H, Hofer D, Hangler HB, et al. Combined CMV prophylaxis improves outcome and reduces the risk for bronchiolitis obliterans syndrome (BOS) after lung transplantation. Transplantation. 2006;81(10):1415–20.
101. Chmiel C, Speich R, Hofer M, Michel D, Mertens T, Weder W, et al. Ganciclovir/valganciclovir prophylaxis decreases cytomegalovirus-related events and bronchiolitis obliterans syndrome after lung transplantation. Clin Infect Dis. 2008;46(6):831–9.
102. Kwakkel-van Erp JM, van de Graaf EA, Paantjens AW, van Ginkel WG, Schellekens J, van Kessel DA, et al. The killer immunoglobulin-like receptor (KIR) group A haplotype is associated with bronchiolitis obliterans syndrome after lung transplantation. J Heart Lung Transplant. 2008;27(9):995–1001.
103. Solidoro P, Libertucci D, Delsedime L, Ruffini E, Bosco M, Costa C, et al. Combined cytomegalovirus prophylaxis in lung transplantation: effects on acute rejection, lymphocytic bronchitis/bronchiolitis, and herpesvirus infections. Transplant Proc. 2008;40(6):2013–4.
104. Ranganathan K, Worley S, Michaels MG, Arrigan S, Aurora P, Ballmann M, et al. Cytomegalovirus immunoglobulin decreases the risk of cytomegalovirus infection but not disease after pediatric lung transplantation. J Heart Lung Transplant. 2009;28(10):1050–6.
105. Paraskeva M, Bailey M, Levvey BJ, Griffiths AP, Kotsimbos TC, Williams TP, et al. Cytomegalovirus replication within the lung allograft is associated with bronchiolitis obliterans syndrome. Am J Transplant. 2011;11(10):2190–6.
106. Kwakkel-van Erp JM, Paantjens AW, van Kessel DA, Grutters JC, van den Bosch JM, van de Graaf EA, et al. Mannose-binding lectin deficiency linked to cytomegalovirus (CMV) reactivation and survival in lung transplantation. Clin Exp Immunol. 2011;165(3):410–6.