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Review Article

Influenza prevention and treatment in transplant recipients and immunocompromised hosts

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The host immune response is critical for the control and clearance of influenza virus after initial infection. Unfortunately, key components of the innate and adaptive responses to influenza are compromised in solid organ and hematopoietic stem cell transplant recipients. As a result, influenza in these key patient populations is associated with prolonged viral shedding, more frequent complications, including bacterial and fungal superinfections and rejection, and increased mortality. While vaccine is the critical prophylaxis strategy in other populations, response rates are diminished, particularly early post-transplant, among immunocompromised patients. Prospective data suggest that antiviral prophylaxis represents an effective and safe alternative to vaccine in patients who would be predicted to have poor responses to influenza vaccine. While there have not been randomized, controlled studies of antiviral therapy completed in solid organ or hematopoietic stem cell patient populations, observational data suggest that early therapy is associated with reduced rates of progression to lower airway involvement, morbidity, and mortality. Further studies are needed to define the optimal regimen, dose, duration, and endpoint to define successful treatment.

Keywords influenza, M2 inhibitors, neuraminidase inhibitors, prevention, transplantation, treatment.

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Introduction

While influenza typically causes acute, self-limited infections in otherwise healthy, immunocompetent patients, influenza is associated with greater morbidity and mortality in addition to markedly prolonged viral shedding among solid organ and hematopoietic stem cell transplant (HSCT) recipients.[1,2] Although there have been several recent epidemiologic studies of influenza in transplant recipients,[3–5] most are focused on lung and HSCT populations. Further, most studies have focused on inpatients and less commonly outpatients with clinically significant disease.[1,2] Most of the existing studies provide limited data on initial clinical presentation and few report serial quantitative virology. Likewise, although there are a number of observational studies of influenza prevention and treatment strategies, few have been randomized, controlled studies.[1,2] As a result, although the safety of available vaccines and antivirals has been described in available studies,[1,6,7] the optimal immunization strategy and appropriate dose and duration of antiviral therapy are incompletely understood.[1,2] In addition, although antiviral resistance is recognized to occur more frequently among transplant patients, the specific risk factors and mitigation strategies to prevent resistance have not been defined.[8] Lastly, although influenza may transmitted from donors, particularly lung donors, the risk of donor transmission of influenza remains poorly defined.[2,9]

Epidemiology and impact

The highest risk of severe influenza appears to be in the early post-transplant period following both HSCT and solid organ transplant (SOT) recipients.[10–12] Allo- and cord blood HSCT recipients appear to be at higher risk of progressive influenza infection then autologous donor transplants.[12] Among HSCT recipient, presence of chronic graft-versus-host disease (GVHD), severe lymphopenia (CD4 $\leq$ 100 cells/ml), unrelated or mismatched donor, and increasing patient age is also associated with progressive influenza and enhanced morbidity and mortality.[4,12,13] Recent data suggest that complications are similar among allo- and autologous stem cell transplant recipients among patients treated with neuraminidase inhibitors.[4] Most severe infections appear to occur early post-transplant, typically within the first 100 days following HSCT. Among SOT recipients, lung transplantation appears to be associated with the highest risk of progression to

pneumonia and morbidity.[1,3,14,15] Interestingly, the risk of influenza appears to be consistent throughout the post-transplant period from longitudinal studies of lung transplant recipients.[14] Additional risk factors among SOT recipients include recent steroid boluses, typically associated with recent rejection, lymphocyte depletion, and young age (especially ≤1 year old).[1–3]

Atypical clinical presentations may be common among transplant recipients. In a study of seasonal influenza among HSCT, fever was present in <30% of patients, sore throat was present in <20%, and myalgias were rarely reported; runny nose (85%) and cough (49%) were the most commonly reported symptoms at presentation.[4,16] During the 2009 pandemic, only 81·1%, 28·7%, and 22·7% of influenza-infected HSCT patients presented with fever, myalgias, and cough, respectively.[4,16] Among SOT recipients during the 2009 pandemic, cough (91·5%) and myalgias (~50%) were frequently present.[3] Fever was more frequent in children (95%) than in adults (80%) as was sore throat (59% versus 37%, respectively).[3]

Influenza is associated with both acute and chronic complications in both SOT and HSCT recipients.[12,17–20] In the acute setting, SOT, especially lung transplant, and HSCT patients have a higher rate of progression to lower tract disease, especially without antiviral treatment.[2,20,21] Without antiviral treatment, mortality is likewise high (25–40%).[2] Transplant recipients also appear to be at higher risk of bacterial and fungal superinfections compared with otherwise healthy patients infected with influenza.[2] There appears to be a small but real risk of acute rejection among SOT recipients during influenza infections, although the host immune response to the virus in lung recipients may be misinterpreted as rejection as there is a predominately lymphocyte infiltrate and evidence of inflammation and associated tissue damage during infection.[20] Several studies indicate that development of chronic rejection (bronchiolitis obliterans syndrome; BOS) occurs more frequently in patients with influenza infection, particularly when it is associated with lower airway involvement.[19,20] Likewise, HSCT recipients may develop late-onset airflow obstruction following influenza infection; this complication is clinically significant and associated with reduced survival.[17,18,21]

Prevention

Vaccination

Although inactivated influenza vaccination is associated with protection against influenza infection and complications of influenza in immunocompetent adults and children,[22] efficacy appears to be reduced in SOT and HSCT recipients.[6,23,24] Among HSCT recipients, exceptionally low rates of response to vaccination have been consistently been demonstrated in the first 6–12 months post-transplant (see Table 1).[25] Compared with healthy controls, antibody responses are reduced at most time points post-transplant.[12,23,25] One study, although, noted a clinical efficacy of 80% among HSCT recipients vaccinated beyond 6 months post-transplant.[26] Among SOT recipients, nearly all studies have demonstrated reduced humoral responses to influenza vaccination as compared to healthy controls.[6] Response rates appear to be lower in patients with higher levels of immune suppression and with recent lymphocyte depletion with the best results generally seen among renal transplant recipients.[6] Even when vaccine elicits humoral responses, peaks of antibody titers and duration of protective titers are reduced compared with healthy controls.[27] Interestingly, even with natural infection, seroprotection levels (36·8%) and influenza-specific CD4+ (50%) and CD8+ (36·4%) interferon-γ T-cell responses are lower than in otherwise healthy persons post-infection.[28] Although influenza vaccination has been consistently found to be safe without a significant enhanced risk of inducing rejection,[6,24] utilization in transplant patients and their recipients remain low (21–94·5%).[29] One small study of heart transplant recipients found influenza vaccination effective in preventing clinical influenza.[30] There is limited data from HSCT or SOT patients to determine whether influenza vaccination can mitigate the severity of infection among vaccinated patients with breakthrough infection.

Table 1. Serologic response to influenza vaccination following hematopoietic stem cell transplantation[25,27,90]

Transplant type	Time post-Tx	A/H1 (%)	A/H3 (%)	B (%)
Auto-HSCT	0 – 12 months	30	32	38
	>12 months	50	50	71
Allo-HSCT	0 – 12 months	31	9	20
	>12 months	13	40	33
Kidney transplant	≥6 months	22·6	41·2	47·1
	<6 months	5·3	21·2	15·8
Lung transplant	≥3 months	30	40	19

Several studies have assessed alternative vaccination strategies, including increased doses of antigen, multiple doses given over time, and intradermal vaccination.[31–33] Available studies have not conclusively demonstrated that alternative strategies of consistently provided higher rates of humoral responses in transplant recipients.[6] A new, high-dose inactivated influenza vaccine has recently been approved for patients ≥65 years old, but studies assessing the efficacy in immunocompromised adults and children are still ongoing.[6] Several groups have recently studied the safety and efficacy of adjuvanted influenza vaccine.[34–40] In general, these vaccines were associated with reduced vaccine responses in transplant recipients compared with healthy controls and the risk of

developing anti-HLA antibodies post-vaccination.[36,39] In one study of heart transplant recipients, there was a higher rate of clinically significant rejection in recipients of the ASO3-adjuvanted vaccine.[39]

Despite the limitations of influenza vaccination, a recent meta-analysis found that it was associated with reduced risk of influenza-like illness and laboratory-confirmed influenza SOT and cancer patients.[24] As such, inactivated influenza vaccination is recommended for both HSCT and SOT recipients, and their close contacts annually by current guidelines.[6,22,23] Live-attenuated, intranasal influenza vaccine is not recommended for post-transplant recipients given the theoretical potential to develop clinical disease from the vaccine strain. Adjuvanted vaccines may be associated with a higher risk of development of anti-HLA antibodies and possibly a higher risk of rejection among heart transplant recipients; this has led some groups to avoid adjuvanted vaccines when unadjuvanted vaccines are available.[6]

Antiviral prophylaxis

As the result of reduced responses to influenza vaccination, many guidelines recommend considering seasonal influenza chemoprophylaxis, particularly in patients early after HSCT or early after receipt of lymphocyte depletion for induction or treatment of rejection among SOT recipients.[22,23,41,42] Multiple randomized trial studies in immunocompetent patients document that antiviral prophylaxis is generally well-tolerated and effective in preventing influenza illness in a variety of settings including in households, chronic care facilities, and the community.[28] Observational reports indicate that outbreak-triggered prophylaxis is protective in high-risk patient populations, including nursing home patients and HSCT recipients.[43,44] A recently published randomized, double-blind, placebo-controlled study provides further evidence to support the use of seasonal prophylaxis in transplant recipients.[7] In this trial, kidney, liver, kidney-liver, and HSCT patients were given 12 weeks of oseltamivir 75 mg QD (or the renally adjusted equivalent) or placebo.[7] Although the study failed to demonstrate superiority of the intervention for the primary endpoint, laboratory-documented, symptomatic influenza infection, most patients with laboratory proven influenza did not present with signs or symptoms of infection. There was a statistically significant reduction in the frequency of culture (0·4% versus 3·8%; 88% protective efficacy) or RT-PCR (1·7% versus 8·4%; 74·9% protective efficacy) proven influenza in favor of seasonal prophylaxis.[7] Of the patients who had breakthrough infection with influenza despite prophylaxis with oseltamivir, none had changes in IC_{50} suggestive of resistance emerging.[7] However, emergence and transmission of oseltamivir-resistant A(H1N1) viruses among contacts in oncology and transplant units have been documented.[45,46] If influenza develops in the setting of oseltamivir prophylaxis, most experts recommend changing to inhaled or intravenous zanamivir treatment until resistance is ruled out. If this occurs in the context of a unit outbreak, then inhaled zanamivir would be the agent of choice for prophylaxis. Despite the data from this study and recommendations in key guidelines, use of seasonal antiviral prophylaxis has been limited by insurance companies refusing to pay for the long-term prophylaxis; wider use of seasonal influenza prophylaxis has been associated with some patients discontinuing therapy because of GI intolerance. Lastly, there is concern, too, that the current regimen may be associated with a low but true risk of resistance emergences. As such, all patients who develop symptoms on prophylaxis should be counseled to seek care immediately and alternative regiments, such as full-treatment dosing should be studied.

Treatment for influenza

Management of influenza in transplant recipients is challenging because modest initial symptom severity and frequency may delay recognition of infection in transplant recipients, as has been discussed above.[16,47] As a result, only a minority of patients have antiviral therapy started within the first 48 h following symptom onset[3,21] although initialing therapy beyond 48 h appears to be effective.[21,42] Further, viral replication is prolonged compared with immunocompetent patients, even when antivirals are utilized. In one study of HSCT recipients with influenza monitored serially by quantitative RT-PCR, all patients had detectable nasal viral RNA for ≥7 days and several had detectability beyond 14 days, despite antiviral therapy in most.[48] Existing data also suggest that most patients receive a short course of therapy (5 days) despite the risk of rebound and, potentially, risk of resistance emergence.[3,49] In addition, it is clear that the immune defect present in each patient is different which likely affects the duration of viral replication. Limited prospective studies in the various transplant populations also leave the optimal dose, regimen, and duration of therapy incompletely defined.[47] Likewise, there is lack of consensus on how response to therapy should be assessed in immunocompromised patients because of the heterogeneity in viral replication and illness severity among these patients.[47] Lastly, emergence of antiviral resistance appears to occur more commonly among immunocompromised patients.[50–52] Resistance appears to be associated with recurrent or worsening symptoms despite ongoing antiviral therapy. Immunosuppressed patients infected with resistant influenza have a higher rate of progression to pneumonia and death, although use of active antiviral therapy has been associated with clinical improvement in some patients.[8,45,46,50,52–54] Unfortunately, specific risk factors for developing resistance and strategies for mitigate development of resistance mutations remain to be defined.[47,50] A novel combination of

amantadine, oseltamivir, and ribavirin has recently been studied in HSCT and holds promise as the combination may prevent the emergence of antiviral resistance.[55]

Despite these limitations, nearly all observational studies of antiviral therapy in SOT and HSCT demonstrate clinical benefit of antiviral therapy compared with no therapy.[4,12,21,56–60] Among HSCT recipients, early antiviral therapy is associated with reduced risk of lower tract disease (adj OR, 0·04; 95% CI, 0·0–0·2; $P < 0·001$), reduced risk of developing hypoxemia (adj OR, 0·14; 95% CI, 0·0–0·4; $P < 0·001$), and reduced overall death at 6 weeks (adj HR, 0·21; 95% CI, 0·0–1·0; $P = 0·049$) and 6 months (adj HR, 0·3; 95% CI, 0·1–0·8; $P = 0·014$).[21] Among SOT patients, early therapy within 2 days of illness onset has been associated with reduced risk of admission to the ICU and enhanced survival.[3] Among lung transplant recipients, antiviral therapy is associated with a high rate of clinical recovery. Although the impact on chronic rejection is less clear, one study of seasonal influenza found that no patients receiving antiviral therapy developed *de novo* BOS or a worsening trajectory of baseline BOS, even when lower tract disease was documented.[15] However, in another study of oseltamivir-treated lung transplant recipients with pandemic A/H1N1 infection, 32% developed BOS or had worsening of baseline BOS.[5] Complications, including bacterial and fungal infections and rejection, appear to occur but may be reduced with antiviral therapy among SOT recipients with influenza treated with antivirals.[3,61–63]

While most recent literature discusses the efficacy of oseltamivir, there are a few case reports that demonstrate tolerability and generally good outcomes with inhaled zanamivir.[64,65] Most of the published experience with zanamivir addresses the compassionate use of its intravenous formulation in patients with progressive influenza infection or documented resistance to oseltamivir.[53,54,66,67] Various mutations leading to resistance have been documented during NAI therapy in immunocompromised hosts, but the most common mutation conferring high-level oseltamivir resistance in N1-containing viruses is the H275Y mutation. Such viruses retain susceptibility to zanamivir but have reduced susceptibility to peramivir. Case reports indicate that IV zanamivir has benefited some transplant patients with oseltamivir-resistant infections, although virus with reductions in susceptibility to all NAIs has emerged in some.[68,69] There are too limited data to make conclusions about efficacy of IV peramivir in this transplant recipients, although virus with the H275Y mutation has emerged or failed to clear during its use.[70–72] Lastly, combination therapy has been tried in a few patients, but additional studies are needed to identify the optimal combination to use.[73] The combination of amantadine, oseltamivir, and ribavirin has shown promise in a small study of HSCT recipients.[55] In contrast, recent studies failed to find improved outcomes with the combination of oseltamivir and zanamivir.[74–76]

A number of investigational antiviral agents are in various stages of clinical development.[77] As several have mechanisms of action that differ from NAIs and M2 inhibitors, they offer the possibility of treating influenza infections resistant to currently available agents. One of these, an inhaled sialidase designated DAS181, shows antiviral activity in uncomplicated seasonal influenza and has been used in treating individual transplant patients with.[78–81] Like intravenous zanamivir, it is currently available on compassionate use basis from its manufacturer.

Donor-derived influenza

Infections present in donors can rarely be transmitted to the recipient of organs or blood products.[82] Influenza, as it may cause lower respiratory illness and rarely extra-pulmonary dissemination, represents a pathogen that could potentially be transmitted from donor to recipient. Data from seasonal influenza epidemics suggest that the detection of influenza RNA-emia is rare in donated blood.[83] US and Japanese studies during the 2009 influenza pandemic failed to demonstrate donors, who developed symptomatic influenza shortly after donation, with detectable RNA-emia.[84,85] Nonetheless, because of the concern of potential transmission, donors of hematopoietic stem cells should not donate if they are symptomatic with influenza.

There have been reports of donor-derived influenza transmission in lung transplant recipients from donors with proven influenza A and B infections.[86–89] Transmission has not been documented in other transplant recipients.[86] The patterns of influenza replication, particularly with novel or avian strains, should be considered in determining the potential risk of transmission in non-lung recipients.[9] If influenza is transmitted through organ donation, viremia and atypical presentations, with limited to no respiratory symptoms, may occur initially in extra-pulmonary transplant recipients.[9] Current guidelines recommend against the use of lung donors with proven influenza until they have received a course of antiviral therapy and optimally have been documented not to have influenza detectable in the lower airways by sensitive assays like RT-PCR. Recipients of any organs from donors infected with influenza should receive 10 days of antiviral treatment at full therapeutic doses.[9]

Conclusions

Influenza causes annual epidemics of respiratory infections that are associated with increased morbidity and mortality in immunocompromised patients. Influenza vaccination is the mainstay of prevention and has been proven to be safe in this unique population. Unfortunately, influenza vaccination is associated with reduced humoral responses, particularly in HSCT recipients early post-transplant. Studies are needed to

optimize vaccine responses in transplant recipients. Furthermore vaccination rates in transplant recipients and their close contacts remain suboptimal. Seasonal prophylaxis with oseltamivir may be an alternative to vaccination in patients who are predicted to have a poor response to vaccine. Therapy with neuraminidase inhibitors, especially when started early, is associated with reduced morbidity and mortality. Prospective studies of antiviral therapy are needed to define the optimal dose, duration, and regimen for treatment for influenza in the various immunocompromised patient populations.

Disclosure

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