

Pneumococcal disease in adult solid organ transplantation recipients

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and mortality ranging from non-invasive to invasive diseases, including pneumonia, bacteremia, and meningitis, with a risk of invasive pneumococcal disease 12 times higher than that observed in non-immunocompromised patients. Moreover, pneumococcal infection has been related to graft dysfunction. Several factors have been involved in the risk of pneumococcal disease in SOT recipients, such as type of transplant, time since transplantation, influenza activity, and nasopharyngeal colonization. Pneumococcal vaccination is recommended for all SOT recipients with 23-valent pneumococcal polysaccharides vaccine. Although immunological rate response is appropriate, it is lower than in the rest of the population, decreases with time, and its clinical efficacy is variable. Booster strategy with 7-valent pneumococcal conjugate vaccine has not shown benefit in this population. Despite its relevance, there are few studies focused on invasive pneumococcal disease in SOT recipients. Further studies addressing clinical, microbiological, and epidemiological data of pneumococcal disease in the transplant setting as well as new strategies for improving the protection of SOT recipients are warranted.

Key words: Transplantation; Pneumococcal infections; Pneumococcal serotypes; Nasopharyngeal carriage; Pneumococcal vaccine

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Core tip: *Streptococcus pneumoniae* causes substantial morbidity and mortality in solid organ transplant (SOT) recipients, ranging from non-invasive to invasive diseases, with a 12-fold risk of invasive pneumococcal disease higher than in non-immunocompromised patients. Pneumococcal vaccination is recommended for all SOT recipients with 23-valent pneumococcal polysaccharides vaccine. Although immunological rate response is appropriate, it is lower than in the rest of the population, decreases with time, and its clinical

Abstract

In solid organ transplant (SOT) recipients, *Streptococcus pneumoniae* can cause substantial morbidity

efficacy is variable. Booster strategy with 7-valent pneumococcal conjugate vaccine has not shown benefit in this population. Despite its relevance, robust evidence on pneumococcal disease in organ transplant recipients is lacking. New strategies for improving the protection of SOT recipients are warranted.

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INCIDENCE

Streptococcus pneumoniae (*S. pneumoniae*) is the cause of 3300 deaths every year in the United States, mainly among adults^[1]. According to the United States Active Bacterial Core Surveillance Database of the Emerging Infections Program Network, in 2012 the incidence of invasive pneumococcal disease (IPD) ranged from 2.8 per 100000 persons aged 18-34 years to 29.6 per 100000 among those older than 65 years^[1]. In the 2013 Annual Epidemiological Report of the European Centers for Disease Prevention and Control (ECDC) the incidence of IPD in Europe was even higher: 3.8 per 100000 persons per year^[2]. Invasive pneumococcal disease is an important cause of illness in patients with certain underlying medical conditions^[3] or demographic risk factors, including age < 2 or ≥ 65 years, chronic diseases, alcohol abuse, smoking, and immunosuppressive conditions such as human immunodeficiency virus (HIV) infection^[4], multiple myeloma, or solid organ transplantation (SOT)^[5-10]. The disease rates for adults with high-risk factors can be more than 20 times that those for adults without high-risk medical conditions. Middle-aged patients with hematological cancer have a rate of IPD of 186 per 100000 persons per year during 2010 and HIV infected patients have a rate of IPD of 173 per 100000 persons per year^[11].

In solid organ transplant recipients, *S. pneumoniae* can cause substantial morbidity and mortality, ranging from no invasive diseases such as otitis media, sinusitis, and non-bacteremic pneumonia to invasive diseases, including bacteremic pneumonia and meningitis^[9]. Data from the literature on SOT recipients are referred almost exclusively to the most severe spectrum of disease. Invasive pneumococcal disease is defined as an isolation of *S. pneumoniae* from a sterile body fluid with a compatible clinical syndrome^[12]. Sterile sites included blood, cerebrospinal fluid, peritoneal fluid, pleural fluid, or needle aspiration of a collection. Sputum or bronchoalveolar lavage isolates are not considered sterile-site isolates in some studies^[13]. The risk of developing invasive pneumococcal disease in these

patients has been estimated in studies carried out in the 70s^[14], 80s^[15], and 90s^[16] to be 2800 per 100000 patient-years in a cohort of kidney transplant recipients^[14], 3600 per 100000 patient-years in heart transplant recipients^[15], and 2270 per 100000 patient-years in lung transplant recipients^[16]. The first two studies were conducted in the pre-vaccine era, justifying higher incidence rates, while in the latter all lung transplant recipients had received pneumococcal vaccine before transplantation. Moreover, in one of the studies most of the kidney recipients were splenectomized, due to the belief at that time that such procedure prolonged graft survival, thus increasing expected IPD cases^[14]. However, it is difficult to compare the findings of these different studies, due to the disparity of vaccination rates, types of organ transplantation, and immunosuppression protocols according to the time when the studies were carried out. A recent study prospectively determined the incidence of IPD in a population of adult SOT recipients over a period of almost 10 years, with an incidence of 146 per 100000 persons per year, 12.8 times greater than that in the general population. Specific incidences for kidney, lung, and liver transplant recipients were 104, 239, and 354 per 100000 transplant recipients per year, respectively, compared to 11.5 cases per 100000 person-years in the general population. Interestingly, there were no cases of IPD in heart and pancreas transplant recipients^[9].

Non-bacteremic pneumococcal pneumonia is the most relevant non-IPD among SOT recipients, due to its morbidity and mortality. *S. pneumoniae* is the second or third leading cause of late community-acquired pneumonia in solid organ transplantation^[17-21]. As in other infections, pneumococcal pneumonia incidence depends on the type of SOT, being more frequent in lung transplant recipients (3262 per 100000 persons-year) followed by kidney (344 per 100000 persons-year) and liver recipients (304 per 100000 persons-year)^[9].

RISK FACTORS OF PNEUMOCOCCAL DISEASE

Several risk factors of pneumococcal disease in SOT recipients have been described. The type of organ transplanted is one of the most important, as previously stated. Liver transplant recipients have an increased risk of IPD, while lung recipients have the highest rates of pneumococcal pneumonia, followed by heart and kidney recipients^[9,16,21].

Time since transplantation is another factor to be considered. The median time since transplantation to the onset of pneumococcal infection is 1.3 to 2.7 years^[9,16,21]. Although Amber *et al.*^[15], in a study carried out in 5 heart recipients, found that the median time for IPD was 58 d (range 1-5 mo), in

most of the studies pneumococcal disease occurs after the first 4 to 6 mo from the transplantation^[9,16]. In a prospective multicenter study carried out in Canada, 57% of the cases were diagnosed during the first three years since transplantation, while one fifth of them occurred after the first 10 years of the transplant^[9].

Although the sizes of most of the studies published are underpowered to establish statistical associations, the type of immunosuppressors has not been related to an increased risk of pneumococcal disease^[9,14-16]. Neither has been found an increased risk of hospital mortality in patients with classic risk factors in the general population, as age, diabetes mellitus, chronic renal disease, or splenectomy^[9]. Probably, the small number of the studies in the literature in this group of immunosuppressed patients and their heterogeneity do not allow drawing appropriate conclusions.

The role of universal prophylaxis with trimethoprim-sulfamethoxazole (TMP/SMX) in the prevention of pneumococcal disease in SOT recipients has not been established. Use of TMP/SMX prophylaxis at the moment of pneumococcal disease diagnosis is common among SOT recipients, with a frequency that ranges from 14% to 100% of the cases. However, the rate of TMP/SMX resistant isolates in these patients is high (66% to 71%)^[9,16]. This high rate of resistance to TMP/SMX invalidates this measure to prevent pneumococcal disease.

Nasopharyngeal colonization is a preliminary step in the development of pneumococcal disease, with transmission only coming from other human carriers^[22]. Pneumococcal colonization has been mainly studied in children, as the highest rates of colonization are found during childhood. As children grow older, the prevalence of pneumococcal carriage decreases, and the distribution of colonizing serotypes changes. With the introduction of the 7-valent pneumococcal conjugate vaccine (PCV7) the colonization rate in children has been reduced from 50%-70%^[23-26] to 21%-33% in the United States and Europe^[27-30]. Pneumococcal colonization studies carried out in children have increased the knowledge about the rate of colonization, the circulating serotypes, the serotypes (mostly encapsulated) related to invasive disease, the expected pattern of resistance and, specially, the effectiveness of the recently introduced new pneumococcal vaccines, offering a better understanding of the pneumococcal disease in the children population^[2,31-33].

There are very few data regarding *S. pneumoniae* nasopharyngeal carriage in healthy adults, showing colonization rates of 4%-13%^[25,34], depending on the geographic area of the population studied^[23,25,26,35-37], and the presence of underlying diseases. Patients with asthma, mainly treated with inhaled corticosteroids, have a higher risk of *S. pneumoniae* colonization than the healthy population^[6,38-40]. In immunosuppressed

patients, the information available is scarce. In HIV-infected adults, the frequency of pneumococcal colonization ranges from 3.4% in United States, to 17% in Brazil and 52% in Malawi^[34,41,42]. No information of pneumococcal colonization in SOT recipients is available.

Influenza activity has been associated with significant increases in the incidence of invasive pneumococcal pneumonia, both in children and adults. The association was more pronounced among younger adults without co-morbidities^[43]. In non-immunocompromised patients, influenza is associated with the greatest increase in the incidence of bacteremic pneumococcal pneumonia caused by serotypes with lower invasive potential. The importance of influenza for adult bacteremic pneumococcal pneumonia varies by serotype and host co-morbidity^[44]. Although there are no studies that address the impact of influenza activity in the incidence of IPD in the transplant setting, it is plausible that there might be a relationship between both diseases.

One of the most important virulence factors of *S. pneumoniae* is the polysaccharide capsule. Chemical and antigenic differences in this capsule result in more than 90 different capsular types or serotypes, 20 of which cause the majority of invasive disease^[45,46]. According to the results of a meta-analysis of adults with pneumococcal bacteremic pneumonia, the risk of death varies with the serotype and is stable among studies across time and in diverse geographic locations. Patients with pneumonia caused by serotypes 3, 6A, 6B, 9N, and 19F died more frequently than those caused by serotype 14. In contrast, patients infected with serotypes 1, 7F, and 8 were significantly less likely to die than those infected with serotype 14^[31]. In a study carried out in Spain, during 2012, the most frequent serotypes linked to IPD in the general population were 1, 3, 7F, 19A, 12F, 14, 22F, 24F, 8, 9A, 4, 10A, and 11A^[46]. In Europe, in adults older 15 years old, the ten most common serotypes of IPD in 2011 ordered by frequency were 7F, 19A, 3, 1, 22F, 8, 14, 12F, 6C and 4, accounting for 61.5% of the typed isolates^[2].

In SOT recipients, serotypes distribution in invasive pneumococcal disease is slightly different from general population. Kumar *et al*^[9] reported that the most frequent serotypes in 21 cases of recent cases of IPD were 23F (4/21, 19%), 22F (3/21, 14.2%) and 19F (2/21, 9.5%), followed by at least one case of 4, 6A, 6B, 8, 9V, 11, 13, 14, 18C and 35V. De Bruyn *et al*^[16] also reported serotype 23F as the most frequent in the IPD occurring in lung transplant recipients (27.2%), followed by 19A (18.1%), 6A/B (18.1%), and at least one case of 3, 4 and 9V. In these more recent studies, serotype of dead patients because of IPD was not specified.

Table 1 Outcome of invasive pneumococcal disease in solid organ transplantation recipients

Ref.	n	Inclusion period	Organ	Time since transplant median (range)	Type of IPD	Prior vaccination	Most frequent isolated serotypes	Graft dysfunction/loss	Mortality
Linnemann <i>et al</i> ^[14]	12	1971-1977	Kidney	No data	Pneumonia: 83% Bacteremia: 41% Meningitis: 16%	No	8, 9, 12, 24	75%/22.2%	8.30% (1/12)
Amber <i>et al</i> ^[15]	5	1985-1987	Heart	0.15 yr (1.2-4.4 mo)	Pneumonia: 80% Bacteremia: 20%	No	3	20%/No data	0%
de Bruyn <i>et al</i> ^[16]	14	1992-2003	Lung	1.3 yr (9.6 mo-2.3 yr)	Pneumonia: 78% Bacteremia: 21%	100%	23F, 19A, 6	No data	7.10% (1/14)
Kumar <i>et al</i> ^[9]	21	1995-2004	Kidney: 11 Liver: 9 Lung: 1	2.7 yr (1.3 mo-23.8 yr)	Pneumonia: 57% Bacteremia: 33% Peritonitis: 5% Parotitis: 5%	23.80%	23F, 22F, 19F	No data	28.60% (6/21)

IPD: Invasive pneumococcal disease.

CLINICAL MANIFESTATIONS

The clinical features of invasive pneumococcal disease in SOT recipients are similar to those of the general population. Bacteremic pneumococcal pneumonia is the most frequent manifestation followed by primary bacteremia and meningitis^[9,14-16]. Kumar *et al*^[9] reported an incidence of 90.5% cases of bacteremia (19/21), 57.1% cases of pneumonia (12/21), and 33.3% cases of primary bacteremia (7/21), with no cases of meningitis. These proportions were similar to those described by de Bruyn *et al*^[16] and Linnemann *et al*^[14], reported 83.3% of pneumonia, 41.6% of bacteremia and 16.6% of meningitis in kidney recipients during the 80s. In the general population in United States, the frequency of bacteremic pneumonia is 69.1%, primary bacteremia 16.8% and meningitis 7%^[1]. By contrast, in the European general population, there is a lower rate of bacteremic pneumonia (48%), with higher rate of primary bacteremia (29%), and meningitis (18%)^[33]. Other rare manifestations of IPD has been previously described in case reports or case series of SOT recipients, including peritonitis or parotitis^[9], endocarditis, spondylitis, and muscle abscess^[47], and necrotizing fasciitis^[48]. Despite its low frequency, reports of sporadic cases highlight an important clinical aspect: *S. pneumoniae* may cause suppurate infection in virtually any anatomic location, with or without prior detected bacteremia.

IMPACT ON PATIENT AND GRAFT SURVIVAL

Invasive pneumococcal disease results in significant morbidity and mortality. Kumar *et al*^[9] reported an in-hospital mortality due to IPD in SOT recipients of 28.6% (6/21), 66.7% (4/6) of them directly attributable to pneumococcal infection. Although they did not find statistically differences of mortality among SOT recipients and non-immunosuppressed patients (28.6% vs 17.8%), this mortality is higher

than that reported in most of the studies carried out in general populations, where the mortality due to pneumococcal bacteremia ranges from 12% to 17%^[49,50].

Length of hospitalization is also higher in SOT recipients (16.2 d vs 11.6 d), probably related to long antibiotics course and complications^[9,16,50]. de Bruyn *et al*^[16] reported more severe complications, requiring mechanical ventilation, in the group of lung transplant recipients who developed bacteremic pneumococcal pneumonia compared with those with non-bacteremic pneumococcal pneumonia. Allograft dysfunction has been associated to pneumococcal infection, as observed with other infections in SOT recipients^[51]. Linnemann *et al*^[14] described a rate of allograft dysfunction in renal transplant recipients with IPD as high as 75% (9/12), with a 22% of cases presenting definitive graft loss (2/9). Amber *et al*^[15] also reported a 20% (1/5) of allograft dysfunction after IPD, in addition to two cases of graft dysfunction treated with increased immunosuppression and complicated with IPD within 20 d. However, graft dysfunction has not been analyzed in the most recent studies of IPD in SOT recipients^[9,16]. Therefore, data available of graft dysfunction are referred exclusively to older studies carried out in heart and kidney transplant recipients and on a small number of patients (Table 1). New prospective studies are required to confirm these data and to analyze the risk of rejection and graft dysfunction in SOT recipients after an episode of IPD.

VACCINATION

Knowledge of the most invasive serotypes allowed the development of the first pneumococcal vaccine. In 1983, a 23-valent pneumococcal polysaccharide vaccine (PPV23) was approved, expanding serotype coverage to more than 85% of the organisms causing IPD^[52]. This vaccine induces a humoral immune response through the production of specific antibodies, but do not prompt immunological

memory. This aspect, added to the fact that PPV23 induced poor T-cell-independent immunogenicity in infants led to development of the pneumococcal conjugate vaccine^[52]. The pneumococcal conjugate vaccine consists of capsular polysaccharides from the most common serotypes that cause IPD along with a carrier protein, and induce a T-cell-dependent immune response, so that they are able to produce immunological memory and greater immunogenic response than that produced by the PPV23^[53]. Another advantage of pneumococcal conjugate vaccine is that stimulates mucosal immunity, resulting in decreased naso-pharynx colonization and also exhibits secondary protection of unvaccinated individuals. Pneumococcal conjugate vaccine (PCV) was initially approved in children less than two years while PPV23 was recommended for children over two years, adults and immunocompromised patients, including SOT recipients.

The first PCV7 was licensed in the United States in 2000 and introduced in Europe in 2001. This vaccine included capsular polysaccharides of serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F, representing approximately 80%-90% of IPD in children. With serotype shifts resulting from vaccine pressure, the protective coverage of PCV7 was reduced, as this vaccine did not include serotypes 1, 3, and 5, which are common in Europe, Asia, and Africa. Therefore, a 13-valent conjugate vaccine (PCV13) including serotypes 1, 3, 5, 6A, 7F, and 19A, was licensed in 2009 in Europe. In 2010, the theoretical vaccine preventable proportion of cases using PCV7, PCV10 and PCV13 in children under five years was 19.2%, 46.1% and 73.1% respectively^[33].

The use of pneumococcal vaccination determined a reduction in the number of cases of invasive and non-invasive pneumococcal disease in children and adults. Several randomized trials and meta-analyses concluded that PPV23 prevents pneumococcal disease in adult population^[54-56]. Other studies suggest that PPV23 protects against invasive infection but not from non bacteremic pneumococcal pneumonia^[56-58] and it did not affect survival^[54]. However, in most of these studies the etiology of community-acquired pneumonia was not confirmed, assuming the expected higher frequency of pneumococcal etiology. In general, studies with more specific endpoints as IPD caused by vaccine serotypes have been more likely to demonstrate efficacy than studies with less specific ones.

In immunosuppressed population, data are scarce and heterogeneous. In SOT recipients, vaccine efficacy is derived from studies conducted mostly in kidney transplant recipients^[59-65] (Table 2), with less information available in heart^[15,66,67] and liver transplant recipients^[68] (Table 3). Moreover, most studies of vaccination in SOT were performed with the old 14-serotypes polysaccharide vaccine (previous to the introduction of the PPV23 in 1980s) and with

different methods for detecting immunity, such as radioimmunoassay. Nevertheless, practically all studies agrees that pneumococcal vaccine in SOT recipients is effective, but the immune response is weaker than in healthy controls and that there is a greater loss of antibodies over time, especially in the first months after the transplant^[59-62,64,65]. Studies carried out in SOT recipients with the PPV23 vaccine yield similar conclusions^[66,68-70]: there was an adequate post-vaccine response but the antibody titers decreased from the sixth month after vaccination^[68,70]. This decrease in the geometric mean titer of antibodies also occurs after the naturally acquired pneumococcal immunity after transplantation^[15]. Interestingly, Blumberg *et al.*^[67] evaluated the impact of prior antibody titers and its relationship with the elicited immune response. In this study, patients with previous antibody titers, although low, obtained better post-vaccine titers after receiving a second vaccine dose (Tables 2 and 3). It is important to emphasize that in all the studies regarding pneumococcal vaccination in SOT recipients, the vaccine was safe, regardless of its effectiveness.

Globally, the knowledge gained from the use of the polysaccharide vaccine in adults reveals that new vaccine strategies are needed to increase vaccine efficacy, especially in vulnerable populations, such as the elderly and immunocompromised patients. In this sense, testing the hypothetical usefulness of the conjugate vaccine (typically used in children) in adult population was performed, supported by the previously discussed benefits. A single study carried out in HIV-infected patients, most of them without antiretroviral therapy, reported protection against pneumococcal disease with PCV7, but not with the polysaccharide vaccine.

Based on these observations, in 2012, the Advisory Committee on Immunization Practices (ACIP) recommended routine PCV13 use for adults aged ≥ 19 years with immune compromise conditions, including SOT recipients, functional or anatomic asplenia, cerebrospinal fluid leaks, or cochlear implants. This vaccine should be administered to eligible adults but in addition to PPV23, the vaccine currently recommended for these groups of adults^[71,72] and SOT recipients, specifically^[73,74]. This strategy appears to be a cost-effective vaccine policy^[75].

However, according to the 2013 ECDC surveillance report, the emergence of non-vaccine serotypes remains an important issue, and continued monitoring in Europe is essential for assessing interventions and informing the development of new vaccines^[2]. This might be especially relevant in the transplant setting. Immunosuppressed patients can have a different serotype distribution than the general population. In a recent study, carried out in Spain, serotypes not included in the PCV13 and

Table 2 Pneumococcal vaccination studies in kidney transplantation in adult recipients

Ref.	N	Time since transplant	Vaccine	Technique	Response to immunization	Long term immune response
Silberman <i>et al</i> ^[59]	27 KT vs 24 healthy adults	7-108 mo	14-valent	Indirect hemagglutination	4-fold increase in titers, equivalent to controls	Not studied
Marrie <i>et al</i> ^[60]	63 KT vs 8 healthy adults	3-99 mo	14-valent	RIA	2.8-fold increase in titers in KT vs 3.4-fold in controls	GMT in KT: 872 ng N/mL post-vaccine 659 ng N/mL at 12 mo
Cosio <i>et al</i> ^[61]	25 KT (14 asplenia) vs 14 healthy adults	3-118 mo	14-valent	RIA	2-fold increase in titers in 93% of 14 healthy adults vs 78% of 14 splenectomized KT and 55% of 11 non-splenectomized KT patients	Not studied
Linneman <i>et al</i> ^[62,63]	104 KT (79 asplenia) vs 33 patients in hemodialysis	No data	14-valent	RIA	1.4-fold increase in antibody titers: 91% GMT post-vaccine with lower response in splenectomized KT vs non-splenectomized KT patients (394 vs 626 ng N/mL, $P < 0.05$) GMT post-vaccine with lower response in KT patients before 6 mo after transplant vs hemodialysis patients (303 vs 592 ng N/mL, $P < 0.05$)	GMT at 24 mo in 33 KT: 932 ng N/mL post-vaccine 385 ng N/mL at 24 mo 536 ng N/mL at revaccination
Arnold <i>et al</i> ^[64]	75 KT (32 asplenia) vs 60 healthy controls	> 12 mo	14-valent	Serum opsonizing antibody	2-fold increase in titers to serotypes 12F and 14 No differences in splenectomized vs non-splenectomized KT recipients	Not studied
Rytel <i>et al</i> ^[65]	61 KT (57 asplenia) vs 23 patients in dialysis vs 9 healthy controls	> 6 mo	14-valent	RIA	Equivalent protective GMT titers vs controls	Equivalent at 1, 2, and 3.5 yr vs controls
Kazancioglu <i>et al</i> ^[69]	21 KT vs 25 healthy controls	> 2 mo	PPV23	ELISA	Protective response to vaccination (40% increases in the antibody concentration) in 95.2% of KT at 1.5 and 3 mo after vaccination	Not studied
Kumar <i>et al</i> ^[78,79]	30 KT (PPV23) vs 30 KT (PCV7)	3 mo-3 yr	PPV23 vs PCV7	ELISA, OPA	Response to at least 1 serotype: no significant differences in antibody titers between PPV23 and PVC7, both using ELISA (53.3% vs 73.3%) and OPA (83.3% vs 80%)	Vaccine responses decline significantly after 3 yr and conjugate vaccine does not improve the durability of response

KT: Kidney transplantation; PPV23: 23-valent pneumococcal polysaccharide vaccine; PCV7: 7-valent pneumococcal conjugate vaccine; RIA: Radioimmunoassay; ELISA: Enzyme-Linked ImmunoSorbent Assay; OPA: Opsonophagocytic assay; GMT: Geometric Mean Titer.

PPV23 formulations were more frequently isolated in patients with IPD and cardio-respiratory comorbidities or immunosuppression, including SOT recipients. Indeed, three serotypes (10A, 11A, and 33F), not included in the PCV13 formulation, were the most frequently isolated in immunocompromised patients with IPD, although their prevalence in the complete cohort was low^[8]. According to Kumar *et al*^[9], only 23.8% of the SOT recipients with IPD had been previously vaccinated with PPV23. In this study, 65% of transplant recipients had disease due to pneumococcus serotypes included in the PCV13 and 85% of them had disease due to serotypes included in the PPV23^[9].

Clinical failure of pneumococcal vaccine is common in the transplant setting. Thus, 24% to 100% of the SOT recipients with pneumococcal disease had being vaccinated^[9,16]. One possible explanation could be the different pneumococcal serotypes distribution observed in the transplant setting and the proportion of serotypes not included

in the pneumococcal vaccine. Other aspect to consider is the reduction in the effectiveness of pre-transplant pneumococcal vaccine in the context of end-organ disease previous to the transplant, as kidney, liver or heart disease, and in the post-transplant due to the use of immunosuppressors necessary to prevent graft rejection, as observed in a study, where all SOT recipients with IPD had received the PPV23 vaccination with all the serotypes producing pneumococcal disease covered by the vaccine^[16]. The required post-transplant immunosuppression may cause progressive decrease of the levels of antibody previously achieved, like other immunizations in SOT recipients, as influenza^[76].

New strategies have been proposed to enhance the immunogenic response and clinical efficacy obtained by PPV23 in SOT recipients, which include revaccination, use of pneumococcal conjugate vaccine, or "booster" strategy. Revaccination with polysaccharide antigens does not elicit a suitable

Table 3 Pneumococcal vaccination studies in heart and liver transplantation in adult recipients

Ref.	n	Type and time since transplant	Vaccine	Technique	Response to immunization	Long term immune response
McCash-land <i>et al</i> ^[68]	25 LT vs 13 healthy controls	LT 1 - 6 mo	PPV23	ELISA	Pneumococcal antibody levels were significantly increased over baseline by 1 mo after vaccination in both groups	At 6th mo: antibody levels declined faster in patients than in control subjects
Amber <i>et al</i> ^[15]	6 HT before and after transplantation	HT 0.6 - 5.3 mo	Unvaccinated	RIA	Protective antibody titers to 12 pneumococcal serotypes contained in PPV23 in a mean of 8.7 ± 1.2 serotypes before transplantation vs 6.5 ± 1.4 serotypes after transplantation ($P < 0.05$)	Not studied
Dengler <i>et al</i> ^[66]	16 HT vs 23 healthy controls	HT > 12 mo	PPV23	ELISA	Protective post-vaccine antibody titers (> 1000 U/mL): 94% in HT recipients vs 100% in controls	Not studied
Blumberg <i>et al</i> ^[67]	35 HT vs 35 healthy controls. Group 2 ($n = 21$), vaccinated before this study The HT patients were classified as: Group 1 ($n = 11$), no vaccinated before this study No data about previous vaccine ($n = 2$)	HT 55 - 122 mo	PPV23	ELISA	Post-vaccine antibody titers were higher in group 2 than in group 1 for all pneumococcal serotypes ($P < 0.05$ for all serotypes, except 3)	Detectable antibody titers at 24 mo (only 7 available patients) in 50% to serotypes 19F and 23F and in 80% to serotype 3

LT: Liver transplantation; HT: Heart transplantation; PPV23: 23-valent pneumococcal polysaccharide vaccine; ELISA: Enzyme-Linked ImmunoSorbent Assay; RIA: Radioimmunoassay.

memory response in healthy people^[77] and kidney recipients respond less vigorously to revaccination than to primary immunization^[63]. Trials comparing PCV7 with PPV23 in renal transplant recipients have not succeeded in achieving differences in immunogenicity between these vaccines^[78,79]. Furthermore, the recommendation made by the ACIP of a prime-boost strategy (PCV13 followed by PPV23 8 wk later) in adult > 50 years old and in immunocompromised patients has been evaluated in SOT recipients with unfavorable results. Kumar *et al*^[80] randomized 130 adult liver transplant recipients to receive either PCV7 followed by a PPV23 booster 8 wk later (the "primed" group) or placebo followed by a standard single dose of PPV23 (the "unprimed" group, as usual practice). There was no difference in immune response between the two groups. More recently, Tobudic *et al*^[81] randomized 80 kidney transplants recipients to received either PCV7 or PPV23 followed by PPV23 the following year. There was no benefit in either of the sequential regimens when compared with single-dose PPV23 vaccination as recommended by the guidelines.

CONCLUSION

S. pneumoniae can cause substantial morbidity and mortality in SOT recipients, ranging from non-invasive to invasive diseases, including bacteremic pneumonia and meningitis, with a 12-fold risk of IPD higher than in non-immunocompromised patients. Despite its relevance, there are few studies focused on IPD in SOT recipients. Pneumococcal vaccination

is recommended for all SOT recipients with PPV23. Although immunological rate response is appropriate, it is lower than that in the rest of the population, decreases with time, and its clinical efficacy is variable. Booster strategy with PCV7 has not shown benefit in this population. Further studies addressing clinical, microbiological, and epidemiological data of pneumococcal disease in the transplant setting as well as new strategies for improving the protection of SOT recipients are warranted.

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