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Review

Pneumococcal vaccination in adult solid organ transplant recipients: A review of current evidence

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ABSTRACT

This narrative review summarizes the current literature relating to pneumococcal vaccination in adult solid organ transplant (SOT) recipients, who are at risk of invasive pneumococcal disease (IPD) with its attendant high morbidity and mortality.

The effect of the pneumococcal polysaccharide vaccine has been examined in several small cohort studies in SOT recipients, most of which were kidney transplant recipients. The outcomes for these studies have been laboratory seroresponses or functional antibody titers. Overall, in most of these studies the transplant recipients were capable of generating measurable serological responses to pneumococcal vaccination but these responses were less than those of healthy controls. A mathematical model estimated the effectiveness of polysaccharide vaccination in SOT recipients to be one third less than those of patients with HIV.

The evidence for the efficacy of the pneumococcal conjugate vaccine in SOT is based on a small number of randomized controlled trials in liver and kidney transplant recipients. These trials demonstrated that SOT recipients mounted a serological response following vaccination however there was no benefit to the use of prime boosting (conjugate vaccine followed by polysaccharide vaccine). Currently there are no randomized studies investigating the clinical protection rate against IPD after pneumococcal vaccination by either vaccine type or linked to vaccine titers or other responses against pneumococcus. Concerns that vaccination may increase the risk of adverse alloresponses such as rejection and generation of donor specific antibodies are not supported by studies examining this aspect of vaccine safety. Pneumococcal vaccination is a potentially important strategy to reduce IPD in SOT recipients and is associated with excellent safety. Current international recommendations are based on expert opinion from conflicting data, hence there is a clear need for further high-quality studies in this high-risk population examining optimal vaccination regimens. Such studies should focus on strategies to optimize functional immune responses.

Contents

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1. Introduction

International guidelines recommend pneumococcal vaccination for solid organ transplant (SOT) recipients to prevent sinopulmonary infection and invasive pneumococcal disease (IPD) [1,2]. Despite these recommendations, coverage with pneumococcal vaccination is suboptimal [3,4]. Pneumococcal polysaccharide vaccination rates have been reported to be 60% in liver transplant recipients [5], and 62% in potential lung transplant recipients [3]. The evidence on which these recommendations are based is limited, with few randomized controlled studies in SOT recipients [6]. This review will summarize the literature regarding the seroresponse data, efficacy, effectiveness and safety of both the polysaccharide and conjugate pneumococcal vaccines in adult SOT recipients.

We searched Cochrane CENTRAL, MEDLINE, EMBASE and The Transplant Library from inception until the 1st of July 2017. We also reviewed article reference lists for additional studies. Literature searches included keywords and free text terms for solid organ transplantation, pneumococcal vaccination and the outcomes of interest. We only included studies that included adult SOT recipients.

This narrative literature review will summarize the current evidence for adult pneumococcal vaccination in SOT recipients.

2. Epidemiology of pneumococcal disease in SOT recipients

The incidence and mortality rate of IPD is higher in SOT recipients than the general population [4,7–11]. The incidence of invasive IPD differs according to transplanted organ but is estimated to be 13–41 times higher than the general population [4,7–11]. Table 1 summarizes the data estimating these risks. The mortality rate from IPD is reported to be 3 times higher in an immunosuppressed population (24%) compared with the general population (9%) [4,7,8]. IPD can occur any time after transplant, however is most common in the first three years post-transplant [7]. Infection with particular pneumococcal serotypes have been associated with different frequency, severity and types of clinical presentations [12]. Serotype 1 has a high invasive disease potential [13] while serotype 3 is associated with an increased case fatality rate compared with other serotypes [14]. Of concern, there is emerging evidence that serotypes not included in currently licensed pneumococcal vaccines are occurring with increased frequency in immunocompromized compared with immunocompetent patients. These include serotypes 6A, 23F, 11A, and 33F [12]. This may relate to clones with capsular types that have a lower relative risk of causing IPD. These serotypes are more opportunistic and primarily affect immunocompromized patients [10,13].

Table 1
Incidence of invasive pneumococcal disease in adult SOT recipients.

Population	First author and year of publication	Incidence of invasive pneumococcal disease
General population	Shigayeva 2016 [8]	4.8 per 100,000 person/years
	Kumar 2007 [7]	11.5 per 100,000 person/years
SOT recipients overall	Shigayeva 2016 [8]	195 per 100,000 person/years[a]
	Kumar 2007 [7]	146 per 100,000 transplanted patients/year
Kidney transplant recipients	Kumar 2007 [7]	104 per 100,000 transplanted patients/year
Lung transplant recipients	Kumar 2007 [7]	239 per 100,000 transplanted patients/year
Heart transplant recipients	Kumar 2007 [7]	0 per 100,000 transplanted patients/year
	Amber 1990 [11]	3600 per 100,000 person/years[b]
Liver transplant recipients	Kumar 2007 [7]	354 per 100,000 transplanted patients/year
Pancreas transplant recipients	Kumar 2007 [7]	0 per 100,000 transplanted patients/year

[a] Includes solid organ and bone marrow transplant recipients.
[b] All pneumococcal infections, not just invasive pneumococcal disease.

3. Pneumococcal vaccinations

When a SOT recipient is exposed to *Streptococcus pneumoniae* though colonization or infection, antibodies are generated against the capsular polysaccharides [15,16]. Pneumococcal vaccination either induces or boosts serotype specific antibody concentrations against these polysaccharides [16]. Pneumococcal polysaccharide vaccines consist of purified pneumococcal polysaccharides that induce a restricted IgG response and do not recruit T cells or generate memory B cells [17]. For pneumococcal conjugate vaccines, the polysaccharides are covalently bound to an immunogenic carrier protein. Peptides from the carrier proteins interact with T cells via Major Histocompatibility Complex (MHC) Class 2 receptors on antigen presenting cells, recruiting T cell responses and promoting B cell differentiation into memory B cells [16,18,19]. Immunosuppressive treatments in SOT recipients are primarily targeted to cellular immunity however both cellular and humoral immune responses may be reduced to varying degrees. Hence, in order to enhance functionality and longevity of antibody responses [16], the ability to induce T cell responses and create immunological memory suggest that the conjugate pneumococcal vaccination may offer advantages over the polysaccharide vaccine [6,20].

4. Laboratory measurement of pneumococcal vaccine responses

Clinical outcomes in efficacy studies of pneumococcal vaccination include IPD (such as blood stream infection or meningitis), non-invasive pneumococcal disease (such as pneumonia) and death [21,22]. The majority of studies of pneumococcal vaccination in SOT recipients have not examined clinical outcomes, rather the surrogate endpoint of laboratory seroresponses to pneumococcal vaccination [23–42]. The most frequently used method is quantification of serotype specific immunoglobulin concentrations pre-and post-vaccination. Functional antibody responses can be measured by opsonophagocytic assays (OPA). OPA may be particularly important in SOT recipients as these assays measure the ability of the antibodies to opsonize and kill pneumococci, which may be affected by the immunosuppression used in transplantation [43–46]. Studies in SOT recipients have examined both antibody titers and opsonophagocytic assay titers [6,20,36,41].

There is reported discordance between antibody concentrations and opsonic concentrations [42].

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