Pneumococcal Infections in Children after Transplantation

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Bacterial infections in recipients of bone marrow and solid-organ transplants remain a major cause of morbidity and death. The cases of 42 children who had undergone transplantation and developed an infection with Streptococcus pneumoniae were retrospectively reviewed. Thirty-four patients had 1 episode of infection, whereas 7 had 2 episodes and 1 had 3 episodes of infection. Solid-organ recipients were more likely to have recurrent invasive disease (P < .02). A total of 31 (74%) of 42 patients were on immunosuppressive therapy, and 74% had been on antimicrobial therapy within 30 days before diagnosis of S. pneumoniae infection. Only 33% of eligible patients had received a pneumococcal vaccine. Twenty-six percent of isolates recovered were not susceptible to penicillin, and 18% were not susceptible to ceftriaxone. Two patients experienced infection-related deaths; one of these had a penicillin-nonsusceptible isolate. The antimicrobial susceptibilities and outcome of infections with S. pneumoniae in patients who have undergone transplantation are similar to those in the general pediatric population.

Infections in recipients of bone marrow and solid-organ transplants remain a major cause of morbidity and death. The type and severity of infection is determined by the organ that is transplanted, the patient’s level of immunosuppression, the intensity of the environmental exposure, and the timing of the infection in relation to transplantation. For patients who have had a good result from transplantation and are at home for months or years on minimal immunosuppressive therapy, infections acquired by the general pediatric population are the most common.

Streptococcus pneumoniae is the most common bacterial pathogen of childhood and is responsible for a wide spectrum of disease, ranging from otitis media to meningitis. It has been demonstrated that antimicrobial-resistant isolates of S. pneumoniae are becoming more common, especially among patients with a history of recent antimicrobial therapy [1]. Transplant recipients have long been recognized as being at risk for the development of invasive disease with S. pneumoniae, because of the immunosuppressive regimens such patients are required to take. Studies elsewhere have shown that infections with S. pneumoniae usually occur at least 3 months after transplantation of bone marrow or solid organs [2–5]. The purpose of our study was...
to better understand the epidemiology and clinical characteristics of pneumococcal disease in patients who have undergone transplantation and to determine whether the increasing incidence of antimicrobial resistance has had an impact on morbidity and mortality rates.

**METHODS**

Since 1993, investigators at each of 8 children’s hospitals in the United States have prospectively identified cases of disease caused by *S. pneumoniae* [1]. For the current study, further demographic and treatment data were gathered retrospectively on transplant patients with *S. pneumoniae* infection identified from 1 September 1993 to 31 December 1998.

Pneumococcal isolates from each center were sent to a central laboratory (Infectious Disease Research Laboratory, Texas Children’s Hospital, Houston), where serogrouping/serotyping and susceptibility testing for penicillin and ceftriaxone were done. Isolates were serogrouped/serotyped by the capsular swelling method by use of commercially available antiserum samples (Statens Seruminstitut and Daco) [6]. Susceptibility testing was performed by standard microbroth dilution with Mueller-Hinton media supplemented with 3% lysed horse blood. Susceptibility was defined according to the 1999 National Committee for Clinical Laboratory Standards guidelines [7]: for penicillin, \( \leq 0.06 \) mg/mL, susceptible; 0.1–1.0 mg/mL, intermediately resistant (hereafter referred to as “intermediate”); and \( \geq 2.0 \) mg/mL, resistant; for ceftriaxone, \( \leq 0.5 \) mg/mL, susceptible; 1.0 mg/mL, intermediate; and \( \geq 2.0 \) mg/mL, resistant. Isolates that were intermediate or resistant to penicillin or ceftriaxone were considered to be nonsusceptible.

The statistical significance of differences in the frequencies of categorical variables was tested with Fisher’s exact test or \( \chi^2 \) test for trends, \( t \) test for comparison of means, and the McNemar test for matched pairs. Two-tailed \( P \) values of \( \leq .05 \) were considered significant. The design of the study did not allow determinations of rates or proportions of pneumococcal infections in transplant patients because information was collected only for patients with pneumococcal infections.

**RESULTS**

The basic demographic data for the 42 patients included in the study are presented in table 1. The median age of the patients when they developed their first infection was 50 months, and the median time after transplant until the development of the first infection was 14 months. Patients who underwent bone marrow transplantation (BMT) were significantly older than those receiving heart (\( P < .003 \)) or liver transplants at the time of their pneumococcal infection (\( P < .03 \)). The median time until the first pneumococcal infection was similar regardless of the type of transplant. All but 2 of the BMTs were allogeneic, and 5 (28%) of the patients had graft-versus-host disease (GVHD) after transplantation. All but 3 patients (2 BMT recipients and 1 liver transplant recipient) underwent a single transplantation before their first infection.

Eleven of the 18 BMT recipients (61%) received no chronic immunosuppressive medications, as compared with the remaining 7 BMT recipients. All solid-organ recipients had received immunosuppressive therapy within 30 days before the development of their infections. There were multiple combinations of immunosuppressive regimens, but the most common chronic transplant medications used either alone or in combination for the remaining 31 patients included prednisone (63%), tacrolimus (43%), cyclosporine (40%), azathioprine (13%), and mycophenolate (10%).

Eleven of the BMT recipients (61%) and 20 of the 24 solid-organ transplant recipients (83%) received antimicrobial therapy within the 30 days before their first pneumococcal infection (\( P = .1 \)). Antimicrobial agents were used for both prophylaxis and acute therapy. Seventeen (53%) of these 31 patients received antimicrobial agents for prophylaxis alone, 7 (22.5%) had received antimicrobial agents for both prophylaxis and acute therapy, and 7 (22.5%) had received antimicrobial agents for acute therapy alone. Agents used for prophylaxis included trimethoprim-sulfamethoxazole (17 patients), penicillin (3 patients), nitrofurantoin (2 patients), dapsone (1 patient), and pentamidine (1 patient). Different \( \beta \)-lactam agents were the most common agents used for acute therapy.

Thirty-three patients were aged \( \geq 24 \) months and therefore were eligible to receive the 23-valent polysaccharide pneumococcal vaccine. Eleven patients (33%) had documentation of receiving the vaccine, but only 3 of these patients received a dose before transplantation. Four patients received their first dose after transplantation but before diagnosis of their first pneumococcal infection, and the remaining 4 received a dose after diagnosis of their pneumococcal infection.

**Focus of infection.** Three patients had a posttransplant history of pneumococcal bacteremia before September 1993 (1 BMT recipient, 1 heart recipient, and 1 kidney recipient), and these episodes were not included in the current data. During the study, 34 patients (81%) had 1 infection, whereas 7 patients (17%; 3 heart recipients, 2 BMT recipients, 1 liver recipient, and 1 kidney recipient) had 2 infections, and 1 patient (2%; heart recipient) had 3 infections, for a total of 51 episodes of pneumococcal infection during the study period. In 44 (86%) of 51 infections, *S. pneumoniae* was isolated from the patient’s blood. Bacteremia occurred alone or in association with other clinical diagnoses such as 7 cases of pneumonia, 5 cases of otitis media, 3 cases of sinusitis, 1 case of meningitis, and 1 case of...
Clinical presentation. The most common clinical signs and symptoms of infection included temperature of $\geq 38.3^\circ C$ (86%), respiratory distress (17%), shock (12%), and petechiae or purpura (7%). Temperature $\geq 38.3^\circ C$ was present in 38% of patients for $< 12$ h, 38% for $12-24$ h, and 21% for $> 24$ h before presentation for medical care. One patient was afebrile.

Treatment and outcome. A total of 29 (57%) of 51 pneumococcal episodes were treated with a parenteral antimicrobial agent followed by orally administered therapy, whereas 19 (37%) of 51 received the entire course of therapy with a parenteral agent. Although several parenteral agents were used, cefotaxime or ceftriaxone were the most common. A total of 3 (6%) of 51 patients were treated with only an orally administered agent (all patients had otitis media). Although several parenteral agents were used, cefotaxime or ceftriaxone were the most common. A total of 3 (6%) of 51 patients were treated with only an orally administered agent (all patients had otitis media). There were 3 deaths among the study patients; 2 were considered to be related to the pneumococcal infection (5%). One BMT patient died of septic shock, 1 kidney transplant recipient died 29 days after admission from complications of sepsis, and the remaining patient (heart recipient) died from an acute episode of rejection within 1 month of pneumococcal disease. Only 1 of these patients was infected with an isolate of $S. pneumoniae$ that was not susceptible to penicillin, and this patient was treated with a cephalosporin. An additional patient had a prolonged hospitalization because of a pleural empyema.

Serogroup/serotype, and antibiotic susceptibility. Forty-five of the 51 isolates (88%) were available for serogrouping/serotyping. The distribution of serogroups/serotypes for the study is shown in table 2. Serotypes 6B, 14, 19F, and 23F accounted for 58% of the isolates. Fifty of the 51 isolates (98%) were available for susceptibility testing. Twenty-six percent of the isolates were not susceptible to penicillin (10% were intermediate and 16% were resistant); 18% were not susceptible to ceftriaxone (10% were intermediate and 8% were resistant). The serogroups/serotypes for the penicillin and ceftriaxone nonsusceptible isolates included 6B, 9V, 12, 14, 19A, 19F, 22, and 23F.

Multiple episodes. Eight patients (19%) had multiple episodes of pneumococcal infection during the review period. Seven patients had 2 episodes (3 heart recipients, 2 BMT recipients, 1 liver recipient, and 1 kidney recipient), and 1 patient had 3 episodes (heart recipient). Recipients of solid-organ transplants were more likely to have recurrent pneumococcal disease than BMT recipients ($P < .02$). The mean time from first to second infections was 5.4 months (range, 1.5–9 months). Six of the 8 patients had bacteremic episodes. One patient had a pneumococcal sinus infection and 6 weeks later developed an episode of bacteremia. One patient had pneumococcal otitis media and 7 months later experienced a second episode of pneumococcal otitis media. Complete serotype data were available for 5 of the patients, all of whom had bacteremic disease. Of the 4 patients who had 1 recurrence, the second infection in all patients was caused by an isolate with a different serotype. The isolate causing the second infection in the single patient who experienced 2 recurrences had the same serotype as the first, but an isolate with another serotype was responsible for causing the third episode of bacteremia. In 4 of these 8 patients, there was no documentation that the 23-valent polysaccharide pneumococcal vaccine had been administered. Of the remaining 4 patients, 2 received the first dose of vaccine before diagnosis of their first infection, and 2 received the vaccine after diagnosis of their first pneumococcal infection.

### Table 1. The demographics of 42 transplant patients with disease due to $S. pneumoniae$ infections.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n = 42)</th>
<th>Bone marrow (n = 18)</th>
<th>Heart (n = 10)</th>
<th>Liver (n = 9)</th>
<th>Kidney (n = 4)</th>
<th>Bowel (n = 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>29</td>
<td>16</td>
<td>5</td>
<td>6</td>
<td>2</td>
<td>0</td>
</tr>
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<td>Female</td>
<td>13</td>
<td>2</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>1</td>
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<tr>
<td>White</td>
<td>22</td>
<td>11</td>
<td>1</td>
<td>6</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>African American</td>
<td>10</td>
<td>2</td>
<td>8</td>
<td>0</td>
<td>0</td>
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<td>Hispanic</td>
<td>7</td>
<td>4</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Median age at first infection, mo (range)</td>
<td>50 (14–244)</td>
<td>101 (23–244)</td>
<td>26 (15–89)</td>
<td>24 (14–137)</td>
<td>65 (37–120)</td>
<td>123 (NA)</td>
</tr>
<tr>
<td>Median time after transplant to first infection, mo (range)</td>
<td>14 (1 day–76)</td>
<td>15 (1 day–54)</td>
<td>17 (5–76)</td>
<td>14 (7–24)</td>
<td>14 (6–76)</td>
<td>5 (NA)</td>
</tr>
</tbody>
</table>

**NOTE.** Data are no. of patients, unless otherwise indicated. NA, not applicable.  
* Significant difference at $P < .003$ compared with patients who received heart transplants and $P < .03$ as compared with patients who received liver transplants.
CD4

GVHD, delayed immune reconstitution with persistently low late infectious complications include the following: chronic worldwide each year [8]. Risk factors for the development of allogeneic and autologous BMTs are performed in children S. pneumoniae after BMT, has continued to increase. It is currently estimated that infections beyond the first year after transplan-

Our data demonstrate that transplant patients usually develop S. pneumoniae infections beyond the first year after transplantation and present with a febrile illness similar to that in children who are not immunosuppressed. Although we found that patients with BMT were much older at the time of their first pneumococcal infection than patients who had undergone heart or liver transplantation, this difference in age probably reflects the various indications for transplantation. Malignancies accounted for 78% of the medical conditions requiring BMT; whereas cardiomyopathies, complex congenital heart disease, and biliary atresia accounted for 84% of the indications for heart or liver transplantation (data not shown). Therefore, patients who received heart or liver transplants required intervention at a much younger age, simply by the nature of their disorders. It is also notable that the frequency of pneumococcal infections in liver and heart transplant recipients may simply reflect the age of the group of patients, which overlaps the peak age at which pneumococcal infections occur in healthy children (6–24 months).

The first successful BMT was performed in the late 1960s. During the past 30 years, the number of BMTs performed yearly has continued to increase. It is currently estimated that >6000 allogeneic and autologous BMTs are performed in children worldwide each year [8]. Risk factors for the development of late infectious complications include the following: chronic GVHD, delayed immune reconstitution with persistently low CD4+ cell counts, and persistent hypogammaglobulinemia (particularly IgG subclass 2) [5, 9]. These factors, combined with impaired opsonization and defective reticuloendothelial function, render these patients highly susceptible to infection with encapsulated bacteria such as S. pneumoniae [10].

In the early years of BMT, adult long-term survivors were identified as being highly susceptible to pneumococcal infection [11]. Although these infections can occur at any time after the BMT, infections due to S. pneumoniae within the first 3 months after transplantation account for <2% of the bacterial infections [12]. In contrast, in a review of infections occurring >3 months after BMT, S. pneumoniae accounted for 15 infections among 113 patients (13.2%) [10]. This was the highest number of infections caused by any single bacterial organism. Infections occurred at a median of 11 months after BMT (range, 4–72 months) and accounted for 5 deaths.

The mortality data obtained in the current study differ from those in the adult BMT experience. Only 1 (6%) of the 18 patients we studied died as a result of pneumococcal infection. This patient was almost 13 years old and had received his transplant ~29 months before presentation with pneumococcal infection. He died within 48 h of onset of bacteremia. The patient experienced complications associated with the transplant, including GVHD, and was maintained on cyclosporine, prednisone, and penicillin prophylix. The organism that caused his bacteremia was resistant to penicillin (MIC, 2 μg/mL) and susceptible to ceftiraxone (MIC, 0.5 μg/mL). In a recent review of fatal pneumococcal infections after allogeneic BMT, only 1 patient was <18 years old [13]. This review described 6 fatal cases of pneumococcal infections among matched sibling allograft recipients who survived for >3 months after transplantation. Five of the patients had chronic GVHD and were receiving immunosuppressive therapy; 4 were receiving antimicrobial prophylaxis. As in the fatal case we studied, this was the first documented pneumococcal infection for each patient.

The occurrence of excessive pneumococcal infections in the recipients of solid-organ transplants has been reported elsewhere [14–17]. Solid-organ recipients are at risk for pneumococcal infections in the second year after transplant and beyond, findings similar to those involving BMT patients. Although the postponement of infection in BMT recipients might reflect use of iv gammaglobulin early in the posttransplant period, most solid-organ recipients are not maintained on extensive immunoglobulin replacement. Only 39% of infected BMT patients were receiving chronic immunosuppressive medications, whereas all of the recipients of solid-organ transplants were receiving such medications. The risk factors for the development of late infections in solid-organ recipients are the patient’s current state of immunosuppression and the intensity of the exposure to potential pathogens [2]. In small studies of

**DISCUSSION**

Our data demonstrate that transplant patients usually develop S. pneumoniae infections beyond the first year after transplantation and present with a febrile illness similar to that in children who are not immunosuppressed. Although we found that patients with BMT were much older at the time of their first pneumococcal infection than patients who had undergone heart or liver transplantation, this difference in age probably reflects the various indications for transplantation. Malignancies accounted for 78% of the medical conditions requiring BMT; whereas cardiomyopathies, complex congenital heart disease, and biliary atresia accounted for 84% of the indications for heart or liver transplantation (data not shown). Therefore, patients who received heart or liver transplants required intervention at a much younger age, simply by the nature of their disorders. It is also notable that the frequency of pneumococcal infections in liver and heart transplant recipients may simply reflect the age of the group of patients, which overlaps the peak age at which pneumococcal infections occur in healthy children (6–24 months).

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**Table 2. Serogroup/serotype of isolates from 51 episodes of pneumococcal disease in transplant recipients, by type of transplant.**

| Type of transplant | 1 | 2 | 3 | 4 | 5 | 6A | 6B | 7 | 8 | 9V | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18C | 19A | 19F | 20 | 22 | 23F | NT |
|--------------------|---|---|---|---|---|----|----|---|---|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| Bone marrow (n = 20) | 0 | 1 | 1 | 0 | 7 | 2 | 0 | 1 | 0 | 0 | 0 | 4 | 0 | 1 | 3 |
| Heart (n = 15) | 0 | 0 | 0 | 1 | 1 | 1 | 3 | 0 | 0 | 5 | 0 | 3 | 0 |
| Liver (n = 10) | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 2 |
| Kidney (n = 5) | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 1 | 0 | 0 | 0 | 1 |
| Bowel (n = 1) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Total, % | 1 (2) | 1 (2) | 1 (2) | 1 (2) | 9 (17) | 2 (4) | 3 (6) | 3 (6) | 5 (10) | 1 (2) | 1 (2) | 10 (19) | 1 (2) | 6 (12) | 6 (12) |

**NOTE.** NT, not typeable or organism could not be grown at reference laboratory.

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adults, the incidences of invasive pneumococcal disease have been calculated at 36 per 1000 patient-years for recipients of heart transplants and 28 per 1000 patient-years for recipients of kidney transplants, both of which exceed the estimated rate for the general public [14, 16].

Surprisingly, recent reviews of pediatric heart transplant recipients have not demonstrated that a large number of patients experience infection with \textit{S. pneumoniae} [18–20]. In one study, of the 210 bacterial isolates obtained from 203 heart transplant recipients who developed infectious complications, only 2 were documented to be due to \textit{S. pneumoniae} [20]. The explanation for the low prevalence of infection is not clear. All of the studies followed patients for at least 2 years (or longer), which would have been ample time to document such an infection, had it occurred. From data generated in the current study, it would appear that this complication might be underreported in pediatric heart transplant patients because 10 patients had invasive disease and 4 of these patients had multiple episodes of bacteremia.

Previous reports of invasive pneumococcal disease among recipients of kidney transplants are confounded by the fact that in 94% of cases, the patients were also asplenic [15, 16]. This was not the case in the current study, in which none of the 4 patients were known to be asplenic. Historically, infections of the genitourinary tract have been the most common infection caused by \textit{S. pneumoniae} recovered from patients in the United States have shown an increasing prevalence of resistance to multiple antimicrobial agents. The nonsusceptible rate has gone from 17.3% to 29.5% for penicillin and from 4.5% to 14.9% for third-generation cephalosporins [25, 26]. The current data demonstrate that the patterns of antimicrobial resistance are similar for these transplant patients, as compared with the general pediatric population.

Recurrent pneumococcal bacteremia is most likely to occur in patients with predisposing conditions [27–30]. It is notable that recipients of solid-organ transplants were more likely to have recurrent bacteremia than BMT patients. Recurrent disease has been demonstrated to occur at any point from 1 day to >6 years from the time of the first infection [29]. Serotyping and DNA fingerprinting of these isolates has demonstrated that ~50% of them represent a new infection [27–29]. The current data show that of the 4 episodes that involved a single recurrence, 100% of paired isolates were discordant. No consistent risk factor could be identified among these patients that would predict a recurrence.

The serotypes encountered among our transplant patients were similar to those reported in immunocompetent patients [31]. All serogroups/serotypes but one (6A) identified in the current study are contained in the 23-valent polysaccharide pneumococcal vaccine, and 78% of them are contained in the 7-valent conjugate vaccine. These data are similar for healthy children in the United States, in whom ~80% of invasive disease is caused by serotypes contained in the 7-valent conjugate vaccine [31]. Unfortunately, only 33% of eligible children had documentation that they had received the 23-valent pneumococcal vaccine, and only 64% of them had received a dose before their first episode of pneumococcal infection. Incomplete documentation of vaccine status may relate to care by multiple physicians; however, these data nevertheless cause concern.

In recipients of BMT, it has been recognized that reimmunization is required for the majority of children because of depletion of T cells and B cells [8]. Recipients of solid organs also present some difficulty because they are maintained on drugs that affect their cell-mediated immunity. Data on these patients demonstrate that by 3 months after transplantation, pneumococcal antibody titers have declined, either because of decreased production or increased clearance of antibodies [14, 32, 33]. Strategies to improve the efficacy of pneumococcal vaccination in solid-organ recipients have met with only limited success in the past. The new protein conjugate pneumococcal vaccines will have increased immunogenicity and stimulate a
memory response. The conjugate vaccine will also have greater potential for a better long-term response, not only in recipients of solid organs but in all transplant patients [34]. The strategy for the use of these vaccines in immunocompromised and immunocompetent children is currently being debated.

Acknowledgments

We thank Linda Lamberth for technical support, as well as the following people, without whose help we could have not conducted this study: Nancy C. Tucker, RN; Andrea Forbes, RN; Micheline Ortenza, Bev Petrites, RN; and Sue Aragon, RN.

References


