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# Bacterial meningitis in solid organ transplant recipients: a population-based prospective study

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**Abstract:** *Background.* Solid organ transplant (SOT) recipients are at risk of infections of the central nervous system. However, the incidence and clinical course of bacterial meningitis in SOT recipients are unclear. We studied occurrence, disease course, and prognosis of bacterial meningitis in SOT recipients in the Netherlands.
*Methods.* All patients with a medical history of solid organ transplantation were selected from our nationwide prospective cohort study on community-acquired bacterial meningitis in patients >16 years old, performed from March 1, 2006 to October 31, 2014. Data on patient history, symptoms and signs on admission, treatment, and outcome were collected prospectively. For transplant recipients, additional information was collected retrospectively.
*Results.* We identified 6 SOT recipients, all receiving renal transplants. The annual incidence of bacterial meningitis was 7-fold higher (95% confidence interval [CI] 2.94–17.02, $P < 0.001$) for renal transplant recipients as compared with the general population (9.56 [95% CI 3.98–22.96] vs. 1.35 [95% CI 1.28–1.43] per 100,000 patients per year). One of the 6 patients (17%) presented with the classic presentation of bacterial meningitis (fever, neck stiffness, and change in mental status). Seizures were common, occurring in 33% of patients. *Streptococcus pneumoniae* and *Listeria monocytogenes* were identified in 2 patients each, and *Escherichia coli* and *Pseudomonas aeruginosa* were both identified once. Four of 6 patients (67%) had an unfavorable functional outcome.
*Conclusion.* Bacterial meningitis is a rare but devastating complication of solid organ transplantation. SOT recipients are at high risk for developing meningitis, and recognition of this condition may be difficult, owing to atypical clinical manifestation.

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Key words: bacterial meningitis; renal transplantation; solid organ transplantation; incidence; prognosis; *Streptococcus pneumoniae*

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Solid organ transplantation is a therapeutic option for organ failure, e.g., kidney, liver, heart, lung, and pancreas. Approximately 289,000 patients have undergone solid organ transplantation in the United States throughout the last 10 years: 167,767 renal transplantations, 64,301 liver transplantations, 23,119 heart transplantations, 16,610 lung transplantations, and 3664 pancreas transplantations (1). In the Netherlands, 8 centers perform transplantations. Approximately 11,000 patients have undergone solid organ transplantation throughout the last 10 years in the Netherlands: 8410 renal transplantations, 1310 liver transplantations, 402 heart transplantations, 961 lung transplantations, and 278 pancreas transplantations (2). During the last few decades, improvements in surgical techniques and immunosuppressive regimens have resulted in improved survival of solid organ transplant (SOT) recipients (3). Previous reports have emphasized the importance of infections of the central nervous system occurring in SOT recipients (4, 5).

However, the incidence of bacterial meningitis in SOT recipients has not been reported. Herein, we determine the incidence and provide a description of disease course and outcome of bacterial meningitis in SOT recipients identified in a nation-wide prospective cohort study on community-acquired bacterial meningitis.

## Methods

We conducted a nationwide, prospective, cohort study on community-acquired bacterial meningitis. Methods have been described previously (6). From this cohort study, we selected all patients with a medical history of solid organ transplantation. Between March 2006 and October 2014, patients >16 years old were included, with bacterial meningitis defined as a positive cerebrospinal fluid (CSF) culture or as a positive blood culture with a relevant pathogen in combination with a CSF pleocytosis of >100 cells/mm$^3$, and clinical presentation compatible with bacterial meningitis. Hospital-acquired meningitis was defined as meningitis during admission or within 7 days after discharge. Patients with a neurosurgical device, neurosurgical operation or procedure, and patients with neurotrauma within 1 month of the onset of meningitis were excluded.

Informed consent was obtained from all participating patients or their legally authorized representatives. The study was approved by the ethical committee of the Academic Medical Center.

Data on patient history, symptoms and signs on admission, laboratory findings, radiologic examination, treatment, and outcome were prospectively collected by means of a case record form. Additional information about the solid organ transplantation was collected retrospectively, including time between transplantation and meningitis, immunosuppressive medication, and vaccination status. Vaccination status included administration of pneumococcal and meningococcal vaccinations, and *Haemophilus influenzae* vaccination in the pre- and post-transplantation period. Vaccination status was ascertained and validated by telephone interview with the transplantation center, treating internal specialist, and general practitioner of the patients. Outcome was graded using the Glasgow Outcome Scale. A favorable outcome was defined as a score of 5, and an unfavorable outcome was defined as a score of 1–4.

The study period from January 2007 to January 2014 was used to calculate the incidence of bacterial meningitis. Dutch population data on SOT recipients at risk during the study period were provided by the Dutch Transplantation Foundation (www.transplantatiesticht ing.nl). Dutch population data were obtained from Statistics Netherlands (7).

Statistical analyses were performed with the use of SPSS statistical software, version 20 (SPSS Inc/IBM). The 95% confidence interval (95% CI) for the incidence and prevalence was calculated using Poisson regression.

## Results

Six of 1449 included episodes of community-acquired bacterial meningitis occurred in 6 SOT recipients (0.4%), all of whom were renal transplant recipients (RTR). Five episodes occurred in the interval from January 2007 to January 2014. In 2007, in the Netherlands, there were 8450 living SOT recipients, which increased up to 10,653 living SOT recipients in 2013. During the interval from January 2007 to January 2014, a total of 68,526 patient-years of follow-up were included. The incidence of bacterial meningitis in SOT recipients was 7.30 per 100,000 patients per year (95% CI 3.04–17.53) and 9.56 per 100,000 patients per year for RTR (95% CI 3.98–22.96). The average incidence of bacterial meningitis in the general population from 2007 to 2014 was 1.35 per 100,000 persons per year (95% CI 1.28–1.43). The incidence of bacterial meningitis was 5.40-fold (95% CI 2.24–12.99, $P < 0.001$) higher for SOT recipients and 7.07-fold (95% CI 2.94–17.02, $P < 0.001$) higher for RTR as compared to the general population.

The median age at the time of meningitis was 65 years (range 36–72 years; 95% CI 51–72 years; Tables 1 and 2) with a median time between organ transplantation and meningitis of 3.5 years (range 1–23 years, 95% CI 0–13 years). Two patients had a distant infection focus (pneumonia, otitis in 1 each) upon presentation. Symptoms were present >24 h in 5 of 6 patients (83%). All patients were on immunosuppressive medication: 2 patients used mycophenolate mofetil, tacrolimus, and prednisone; and the combinations of azathioprine and cyclosporine, azathioprine and prednisone, cyclosporine and prednisone, and mycophenolate mofetil, cyclosporine, and prednisone were used by 1 patient each. Two patients used prophylactic antibiotic (norfloxacin, trimethoprim-sulfamethoxazole [TMP-SMX] in 1 each). Vaccination status could be retrieved for 5 of the 6 patients: none were vaccinated against pneumococci, meningococci, or *H. influenzae* before or after the transplantation.

Classic symptoms and signs of bacterial meningitis were relatively uncommon: headache occurred in 3 of 6

**Clinical characteristics of solid organ transplant recipients with meningitis[1]**

| Characteristic | *n* (%) |
|---|---|
| Age, years (range) | 65 (37–72) |
| Years since transplantation (range) | 3.5 (1–23) |
| Female | 2 (33) |
| Predisposing factors[2] | 3 (50) |
| Otitis media | 1 (17) |
| Diabetes mellitus | 2 (33) |
| Symptoms and signs on admission | |
| Duration of symptoms, >24 h | 5 (83) |
| Headache | 3 (50) |
| Nausea | 3 (50) |
| Fever | 4 (67) |
| Triad[3] | 1 (17) |
| Neck stiffness | 3 (50) |
| Seizures | 2 (33) |
| Signs of septic shock | 2 (33) |
| Altered mental state (EMV <14) | 4 (67) |
| Coma (EMV <8) | 3 (50) |
| Focal neurological deficits | 2 (33) |
| Radiological examination | 5 (83) |
| Intracerebral hemorrhage | 1 (20) |
| Mastoid opacification | 1 (20) |
| Blood chemistry tests | |
| Leukocyte count (cells/mm$^3$) | 15.5 (8.5–28.3) |
| C-reactive protein (mg/L) | 240 (28–397) |
| Indices of inflammation in CSF | |
| Leukocyte count (cells/mm$^3$) | 713 (17–12,014) |
| Granulocytes (%) | 85 (73–99) |
| Protein (g/L) | 3.9 (1.4–6.0) |
| CSF/blood-glucose ratio | 0.04 (0.0–0.89) |
| CFS culture | |
| *Streptococcus pneumoniae* | 2 (33) |
| *Listeria monocytogenes* | 2 (33) |
| *Pseudomonas aeruginosa* | 1 (17) |
| *Escherichia coli* | 1 (17) |
| Complications | |
| Seizures | 2 (33) |
| Hearing impairment | 1 (17) |
| Cerebral infarction | 1 (17) |
| Outcome | |
| Favorable outcome | 3 (50) |
| Mortality | 2 (33) |
| Sequelae | 3 (17) |

[1]Data are presented as *n* (%) or median (range).
[2]Other than transplantation.
[3]Triad of fever, neck stiffness, and change in mental status.
CSF, cerebrospinal fluid; EMV, Glasgow Coma Scale.

*Table 1*

(50%) of episodes, neck stiffness in 3 of 6 (50%), fever in 4 of 6 (67%), and a change in mental status (defined by a Glasgow Coma Scale score <14) in 4 of 6 (67%) patients. One patient presented with the classic triad of fever, neck stiffness, and a change in mental status. Generalized seizures occurred in 2 of 6 (33%) patients.

Neuroimaging (computed tomography) was performed on admission in 5 of 6 patients (84%; Table 3). Abnormalities were found in 2 patients (mastoiditis and generalized brain edema in 1 patient each). Lumbar puncture was performed in all patients. CSF white blood cell counts were <1000 cells/mm$^3$ in 4 of 6 patients (67%). One patient presented with only 17 cells/mm$^3$ and was eventually diagnosed with pneumococcal meningitis, based on a positive CSF culture. All patients had 1 or more individual CSF predictors of bacterial infection (glucose level <1.9 mmol/L, blood-glucose ratio <0.23, protein level >2.2 g/L, >2000 $\times$ 10$^6$/L leukocytes, or >1180 $\times$ 10$^6$/L polymorphonuclear leukocytes) (8).

CSF cultures revealed *Streptococcus pneumoniae* and *Listeria monocytogenes* in 2 patients each, and *Escherichia coli* and *Pseudomonas aeruginosa* were identified in 1 patient each. CSF Gram stain showed bacteria in 3 of 6 patients (2 with *S. pneumoniae* and 1 with *P. aeruginosa* meningitis). Four patients were initially treated with the combination of ceftriaxone plus penicillin/amoxicillin, 1 with ceftazidime plus linezolid, and 1 patient with co-amoxiclav (Table 3). Adjunctive dexamethasone was administered in 3 of 6 patients (50%); in 2 patients, dexamethasone (4 times a day 10 mg) was started together with the antimicrobial treatment, and in 1 patient, dexamethasone was started after the initiation of antimicrobial treatment.

During their clinical course, 2 patients developed seizures; 1 of these patients had generalized seizures, the other had focal seizures and was diagnosed with a

**Patient characteristics and clinical presentation of bacterial meningitis in solid organ transplant recipients**

| Patient no./year of Tx | Organ | Indication | Age at episode of meningitis (years) | Time from transplant to infection (years) | Medication | Presenting symptoms | Duration of symptoms (days) | Body temperature (°C) | Neck stiffness | Decrease of consciousness | Focal signs | Vaccination[1] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1/1999 | Kidney | Renal failure of unknown etiology | 72 | 7 | Azathioprine/ cyclosporine/ norfloxacin | Nausea/otitis | 1 | 39.9 | Yes | Yes | No | No |
| 2/1984 | Kidney | Interstitial nephritis | 36 | 23 | Azathioprine/ prednisone | Headache/ seizure | 3 | 36.0 | No | Yes | Yes | Unknown |
| 3/2007 | Kidney | Hypertensive nephrosclerosis | 67 | 1 (13 months) | MMF/ cyclosporine/ prednisone | Nausea/ confusion/ diarrhea | 5 | 35.3 | Yes | No | No | No |
| 4/2004 | Kidney | Diabetic nephropathy | 62 | 5 | MMF/tacrolimus/ prednisone TMP-SMX | Headache/ nausea | 4 | 40.2 | No | Yes | No | No |
| 5/2008 | Kidney | IgA nephropathy | 63 | 2 | Cyclosporine/ prednisone | Seizure/ pneumonia | 4 | 38.8 | No | Yes | Yes | No |
| 6/2009 | Kidney | Ischemic nephropathy | 71 | 2 | MMF/tacrolimus/ prednisone | Headache | 2 | 39.3 | Yes | No | No | No |

[1]Vaccination against pneumococci, meningococci, or *Haemophilus influenzae* before or after the transplantation.
No., number; Tx, transplantation; IgA, immunoglobulin-A; MMF, mycophenolate mofetil; TMP-SMX, trimethoprim-sulfamethoxazole.

***Table 2***

*Table 3*

**Ancillary examination and outcome of bacterial meningitis in solid organ transplant recipients**

| Patient | Neuroimaging results | CSF leukocytes/ µL | CSF protein g/L | CSF glucose mmol/L | Causative organism | Initial treatment | Treatment after result CSF culture | Complications | Sequelae |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Opacification right-sided mastoid consistent with mastoiditis | 1280 | 3.98 | <0.1 | *Streptococcus pneumoniae* | Ceftriaxone/ampicillin/ metronidazole/ dexamethasone | Penicillin | Generalized seizures | Cognitive impairment |
| 2 | Generalized edema | 17 | 5.94 | <0.1 | *S. pneumoniae* | Co-amoxiclav | Co-amoxiclav | None | Death |
| 3 | Normal CT | 12,014 | 3.89 | 0.8 | *Escherichia coli* | Ceftriaxone/penicillin/ dexamethasone | Ceftriaxone | Hearing impairment | Hearing impairment |
| 4 | Normal CT | 660 | 2.70 | 12.5 | *Listeria monocytogenes* | Ceftriaxone/amoxicillin/ dexamethasone | Amoxicillin | None | None |
| 5 | Normal CT | 765 | 5.94 | <0.1 | *Pseudomonas aeruginosa* | Ceftazidime/linezolid | Amoxicillin | Intracerebral hemorrhage/ focal seizures | Death |
| 6 | Not performed | 570 | 1.43 | 0.4 | *L. monocytogenes* | Ceftriaxone/amoxicillin | Amoxicillin | None | None |

CSF, cerebrospinal fluid; Co-amoxiclav, amoxicillin/clavulanic acid; CT, computed tomography.

subarachnoid hemorrhage as a complication of *P. aeruginosa* meningitis. Unfavorable outcome occurred in 4 of 6 patients (67%); 2 patients died, and 2 surviving patients suffered from sequelae (hearing loss and cognitive impairment in 1 patient each) (Table 3).

## Discussion

Our study shows that SOT recipients have an increased risk of bacterial meningitis. Previous reports have emphasized the importance of infections of the central nervous system after solid organ transplantation. Despite the identified increase in risk, bacterial meningitis is an uncommon disease in transplant recipients.

Patients presented with few classic symptoms and signs of bacterial meningitis, and only 1 patient had the classic triad of fever, impaired consciousness, and neck stiffness. The patients often had a more protracted clinical course compared to the general bacterial meningitis population, with symptoms for several days (9). This pattern of prolonged duration of disease and absence of typical clinical characteristics has previously been recognized for *L. monocytogenes* meningitis (10). In that study, prolonged duration of disease was associated with less marked CSF abnormalities, which was also found in RTR with bacterial meningitis. The combination of few typical signs of meningitis and CSF abnormalities may hinder recognition of bacterial meningitis in SOT recipients. To prevent diagnostic delay, a low threshold should be kept for performing a lumbar puncture in RTR, even in those with a low suspicion of bacterial meningitis.

Most common causative pathogens of bacterial meningitis in SOT recipients were *S. pneumoniae* and *L. monocytogenes*. *L. monocytogenes* meningitis has been described to occur more frequently in immunocompromised and elderly patients (10). Furthermore, *L. monocytogenes* is a well-known causative organism of systemic infection and bacterial meningitis in post-transplantation patients. A study of *Listeria* infections in 24 SOT recipients showed a 110-fold increased risk of Listeria infections compared to the general population (11). This increased risk may explain the different spectrum of causative organisms in our cohort of SOT recipients.

Two cases were caused by *E. coli* and *P. aeruginosa*, both of which are rare causes of community-acquired bacterial meningitis, described in only 0.7% and 0.07% of all cases (9). Meningitis caused by *E. coli* and *P. aeruginosa* is usually described in patients with bacteremia

and other foci of infection, consistent with our patients (12). Based on our findings, empiric treatment for transplant patients should be broad and include at least amoxicillin for *Listeria* coverage and an extended-spectrum cephalosporin. As ceftriaxone is not effective against *Pseudomonas*, ceftazidime should be considered instead.

Antimicrobial prophylactic strategies have led to a decline in the incidence of several opportunistic infections in SOT recipients. One RTR in our cohort had *L. monocytogenes* meningitis despite using TMP-SMX. Prophylactic antibiotic treatment with TMP-SMX has been described to reduce the risk of *L. monocytogenes* infection (12). However, the use of TMP-SMX does not rule out *L. monocytogenes* as a causative organism of bacterial meningitis.

All identified episodes of bacterial meningitis were in the late post-transplantation period (after 6 months). Infections in the first month after solid organ transplantation are usually nosocomial, procedure-related, or donor-derived infections. From 1–6 months after transplantation, infections are opportunistic or caused by activation of latent infections, as a result of the effect of immunosuppression. After 6 months, the risk of infections diminishes as immunosuppression is tapered. However, SOT recipients have a persistently increased risk of infection from community-acquired pathogens, as a result of prolonged used of immunosuppressive agents (13).

Half of our patients were treated with adjunctive dexamethasone therapy. The use of dexamethasone in bacterial meningitis has been proven effective in patients in high-income countries with *S. pneumoniae* meningitis (14); however, no effect has been established in patients with *L. monocytogenes* meningitis or in immunocompromised patients with human immunodeficiency virus infection (15). As RTR were found to have a different spectrum of causative microorganisms, it is unclear whether adjunctive dexamethasone has a role in the treatment of SOT patients.

We found that none of the patients was vaccinated before or after transplantation. Organ transplant recipients have an increased greater lifetime risk of vaccine-preventable diseases. A prospective population-based surveillance study showed a 13-fold higher risk of invasive pneumococcal disease in patients after organ transplantation, compared with the general population (16). The response to vaccines depends on a functioning immune system, which is impaired in patients on dialysis or after solid organ transplantation. Multiple-vaccination schemes have been proposed, consisting of 7-valent pneumococcal conjugate vaccine (PCV-7) or 23-valent pneumococcal polysaccharide vaccine (PPV-23), or a combination of both (17). A 2013 systematic review found serologic response rates for *S. pneumoniae* vaccines to be 83%, and no difference was found between PCV and PPV (18). A 2012 randomized controlled trial evaluated the use of a boost with PCV follow by PPV or PPV alone. This trial identified no differences in immune response with either scheme. The optimal vaccination scheme for transplant patients is currently unclear. International guidelines recommend vaccination with 13-valent pneumococcal conjugate vaccine followed 8 weeks later by PPV-23 (18, 19).

A limitation of this study is the low number of patients identified with bacterial meningitis after solid organ transplantation, increasing uncertainty about the general applicability of the results, and precluding direct comparisons with non-SOT bacterial meningitis patients. Still, we believe that this study provided valuable information on bacterial meningitis in SOT recipients.

In conclusion, bacterial meningitis is a rare but devastating complication of solid organ transplantation. SOT recipients are at high risk for developing meningitis, and recognition of this condition may be difficult, owing to atypical clinical manifestation.

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