Rhodococcus Infection in Solid Organ and Hematopoietic Stem Cell Transplant Recipients


We conducted a case–control study of 18 US transplant recipients with Rhodococcus infection and 36 matched controls. The predominant types of infection were pneumonia and bacteremia. Diabetes mellitus and recent opportunistic infection were independently associated with disease. Outcomes were generally favorable except for 1 relapse and 1 death.

Rhodococcus, a gram-positive cocccobacillus, has been isolated from water, soil, and the manure of herbivores. It is a facultative intracellular pathogen that survives in host macrophages. Immunosuppressive medications that compromise cell-mediated immunity can predispose to infection (1,2).

Our knowledge of disease characteristics among transplant recipients is limited to case reports (3–8). With the increase in organ transplantation and improved survival of transplant recipients, the incidence of disease will likely increase in the coming years. In this study, we sought to describe characteristics, risk factors, and outcomes of Rhodococcus infection among solid organ transplant (SOT) and hematopoietic stem cell transplant (HSCT) recipients in the United States.

The Study
We conducted a case–control study at 8 US medical centers during January 2000–December 2012. The study was approved by appropriate Institutional Review Boards. Case-patients were those with clinical or radiographic features of infection and positive culture results for Rhodococcus spp. Identification of the organism was performed by using biochemical methods at microbiology laboratories of participating institutions. At the discretion of laboratory staff, identification was confirmed by using 16S rRNA sequencing.

Controls received a similar organ within 3 months before or after the index case-patient at the same center and did not show Rhodococcus infection. Each case-patient was matched with 2 controls. Allogeneic and autologous HSCT recipients were matched to recipients of the same type.

We used descriptive statistics to summarize results for the cohort. Conditional logistic regression was used to evaluate risk factors for infection. Factors associated with disease less than the 0.10 significance level for univariate analysis were included in the multivariate model. Statistical software Stata/SE version 13.1 (StataCorp LP, College Station, TX, USA) was used.

We identified 18 patients with Rhodococcus spp. infection (Table 1, https://wwwnc.cdc.gov/EID/article/23/3/16-0633-T1.htm). Mean age was 55 (range 3–78) years. Six patients underwent HSCT (5 allogeneic, 1 autologous) and 12 SOT (4 heart, 4 lung, 3 kidney, 1 liver). Median time from transplant to infection was 5 (range 2–54) for HSCT recipients and 28 (range 3–237) months for SOT recipients. Infection occurred within the first year posttransplant for half of the patients. Five (39%) of 13 patients were living on a farm or had known contact with horses; exposure history was unknown for 5 patients.

Median time to diagnosis after onset of symptoms was 20 (range 2–67) days. This median was determined mainly by the time that the patient sought medical attention and the time of clinical specimen collection. At the time of diagnosis, 3 (17%) patients were managed in outpatient settings, 12 (67%) in inpatient wards, and 3 (17%) in intensive care units.

The predominant infections were pneumonia (61%, 11/18) and bacteremia (56%, 10/18). Bacteremia was secondary to pneumonia for 4 patients and catheter-associated for 4 patients. Fever occurred in half of the patients. Patients with pneumonia had dyspnea (45%, 5/11), cough (70%, 7/10), sputum production (20%, 2/10), and chest

1Results from this study were presented in part at IDWeek 2012, October 17–21, 2012, San Diego, California, USA.

2Current affiliation: University of Manchester, Manchester, UK.
pained (30%, 3/10). None had hemoptysis. Lung disease was
infiltrative in 8/11 (73%) patients, nodular in 8/11 (73%), and
cavitary in 2/11 (18%). Median neutrophil count at
diagnosis was 4,133/mm³ (range 532–16,468/mm³), and
median lymphocyte count was 705/mm³ (range 90–3,350/
mm³). Species identification was performed for 9 isolates
(8 R. equi and 1 R. corynebacterioides). We found no sig-
nificant difference in incidence of preceding opportunistic
infection between SOT and HSCT recipients (33% vs. 50%; p = 0.62).

Infected patients were matched with 36 controls. Uni-
ivariate analysis showed that type of immunosuppression,
augmented immunosuppression, increased levels of tacro-
limus or cyclosporine, and trimethoprim/sulfamethoxazole
(TMP/SMX) prophylaxis were not associated with infe-
tion. Multivariate analysis showed that diabetes mellitus
(p = 0.041) and recent opportunistic infection (p = 0.045)
were independently associated with infection (Table 2).

All isolates tested were susceptible to vancomy-
cin (5/5), rifampin (5/5), linezolid (9/9), and imipenem
(7/7). Fourteen percent (1/7) were susceptible to amoxi-
cillin/clavulanate; 29% (2/7) to ceftriaxone; 55% (6/11)
to TMP/SMX; 70% (7/10) to tetracycline or minocycline;
75% (6/8) to azithromycin or clarithromycin; and 80%
(7/7) to levofloxacin, moxifloxacin, or gatifloxacin. Four
isolates were resistant to penicillin and 1 was resistant
to clindamycin.

Most patients received combination treatment with
2–3 antimicrobial drugs (Table 1). Most commonly used
drugs in the initial regimen were vancomycin, a fluoro-
quinolone, or a carbapenem. Median duration of treatment
was 1 month (range 2 weeks–7 months) for patients with
catheter-associated bacteremia and 6 months (range 2–60
months) for patients with all other infections. Immunosup-
pression was decreased in 44% (7/16). The patient with a
pacomaker pocket infection had the device removed.

Median follow-up period was 17 (range 1–84) months.
One allogeneic HSCT recipient with R. equi pneumonia
died of respiratory failure 13 days after diagnosis. He was
receiving effective treatment with levofloxacin and TMP/
SMX. One allogeneic HSCT recipient with bacteremic
cavitary pneumonia who received 6 months of antimicro-
bial drug treatment had disease relapse (fever, cough, and
dyspnea) 9 months after initial presentation. Rhodococcus
spp. were recovered from bronchoalveolar lavage fluid at
relapse. The 4 patients with catheter-associated bacteremia
had their catheters removed and did not show relapse.

Conclusions
Our study showed an association between Rhodococcus infec-
tion and preceding opportunistic infection. This finding
suggests that affected patients have a high net state of im-
munosuppression. Prior cytomegalovirus infection, the most
common opportunistic infection in the study, might have had
an immunomodulatory effect that made patients more likely
to show development of a second opportunistic infection.

Most patients were not neutropenic at diagnosis, con-
sistent with the fact that Rhodococcus spp. affect mainly
patients with impaired cell-mediated immunity. TMP/
SMX prophylaxis did not confer protection, probably be-
cause of high resistance rates. Patients did not always have
a history of exposure to livestock as previously described
(2). Median time to infection was shorter for HSCT re-
cipients, probably because catheter-associated bacteremia

Table 2. Univariate analysis of risk factors associated with Rhodococcus infection in solid organ and hematopoietic stem cell
transplant recipients, United States

<table>
<thead>
<tr>
<th>Variable</th>
<th>Case-patients, n = 18</th>
<th>Control patients, n = 36</th>
<th>Univariate OR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y (range)</td>
<td>55 (3–78)</td>
<td>50 (2–78)</td>
<td>1.05 (0.99–1.11)</td>
<td>0.13</td>
</tr>
<tr>
<td>Male sex</td>
<td>12/18 (66.7)</td>
<td>22/36 (61.1)</td>
<td>1.21 (0.42–3.45)</td>
<td>0.72</td>
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<tr>
<td>White race</td>
<td>15/18 (83.3)</td>
<td>23/36 (63.9)</td>
<td>3.17 (0.65–15.43)</td>
<td>0.15</td>
</tr>
<tr>
<td>Diabetes mellitus†</td>
<td>9/16 (56.0)</td>
<td>6/34 (17.6)</td>
<td>9.90 (1.20–81.62)</td>
<td>0.03</td>
</tr>
<tr>
<td>Chronic kidney disease‡</td>
<td>3/16 (18.8)</td>
<td>5/35 (14.3)</td>
<td>1.15 (0.19–7.03)</td>
<td>0.88</td>
</tr>
<tr>
<td>Immunosuppressant</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>10/18 (55.6)</td>
<td>25/35 (71.4)</td>
<td>0.15 (0.02–1.39)</td>
<td>0.10</td>
</tr>
<tr>
<td>Sirolimus</td>
<td>3/18 (16.7)</td>
<td>2/35 (5.7)</td>
<td>4.65 (0.46–46.89)</td>
<td>0.19</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>10/18 (55.6)</td>
<td>18/35 (5.4)</td>
<td>1.36 (0.20–9.0)</td>
<td>0.75</td>
</tr>
<tr>
<td>Prednisone</td>
<td>13/18 (72.2)</td>
<td>25/35 (71.4)</td>
<td>1.00 (0.25–4.0)</td>
<td>1.00</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>2/18 (11.1)</td>
<td>3/35 (8.6)</td>
<td>2.00 (0.13–31.98)</td>
<td>0.62</td>
</tr>
<tr>
<td>Increased calcineurin inhibitor level§</td>
<td>2/13 (15.4)</td>
<td>4/32 (13.3)</td>
<td>1.20 (0.16–9.20)</td>
<td>0.86</td>
</tr>
<tr>
<td>History of allograft rejection¶</td>
<td>2/12 (16.7)</td>
<td>1/24 (4.2)</td>
<td>4.00 (0.36–44.11)</td>
<td>0.26</td>
</tr>
<tr>
<td>Augmented immunosuppression¶</td>
<td>7/18 (38.9)</td>
<td>13/37 (35.1)</td>
<td>1.28 (0.24–6.89)</td>
<td>0.77</td>
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<tr>
<td>TMP/SMX prophylaxis</td>
<td>10/18 (55.6)</td>
<td>19/36 (52.7)</td>
<td>1.15 (0.33–4.03)</td>
<td>0.83</td>
</tr>
<tr>
<td>History of opportunistic infection¶</td>
<td>7/18 (38.9)</td>
<td>4/36 (11.1)</td>
<td>10.57 (1.25–89.0)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

*Values are no. (%) unless otherwise indicated. OR, odds ratio; TMP/SMX, trimethoprim/sulfamethoxazole.
†Requiring treatment with oral anti-diabetic agent(s) or insulin.
‡Creatinine level >2 mg/dL.
§Tacrolimus >12 μg/mL or cyclosporine >250 μg/mL in the preceding 30 days.
¶Use of corticosteroid pulses, alemtuzumab, anti-thymocyte globulin, basiliximab, or rituximab in the 6 months preceding infection.
#Opportunistic infections in case-patients were cytomegalovirus viremia (3) or invasive disease (2), pulmonary aspergillosis (1), and BK polyomavirus–
associated hemorrhagic cystitis (1).
was more common among these patients. Predominantly among SOT recipients, infection occurred late after transplant (>12 months), and none of the infections were catheter-associated (2).

For systemic infections, monotherapy might result in emergence of resistance. In a report from Taiwan, 3 of 7 R. equi isolates had inherent concomitant resistance to all β-lactams, macrolides, and rifampin (9). We did not observe this multidrug-resistance pattern. For transplant recipients with systemic infection, we recommend combination treatment with 2–3 antimicrobial drugs (vancomycin, fluoroquinolone, or carbapenem). TMP/SMX and clindamycin should be avoided in empiric treatment regimens because of variable rates of susceptibility. Macrolide antimicrobial drugs, except for azithromycin, decrease the metabolism of cyclosporine, tacrolimus, sirolimus, and everolimus. Conversely, rifampin increases the metabolism of these drugs. These interactions should be considered when treating transplant recipients. Rhodococcus spp. can also form adherent biofilms (10). Thus, removal of central catheters is imperative in the management of infected patients.

We observed only 1 death attributable to infection in an HSCT recipient. This finding differs from an attributable mortality rate of 34.3% in a multicenter study of 67 patients with AIDS (mean CD4 cell count 35/µL) (11). The higher mortality rate probably reflects the degree of immunosuppression among patients with advanced HIV infection and close clinical monitoring of transplant recipients, which enables timely management. Death and relapse rates in our series were comparable with those in a review of 30 cases (2).

Our retrospective study had inherent limitations related to collection of data. In the analysis, we included SOT and HSCT recipients who differed in underlying disease states and immunosuppression. The study was also limited by the relatively small number of cases. This limitation was also reflected in wide CIs in risk factor analysis. However, we showed that risk factors for Rhodococcus infection were diabetes mellitus and recent opportunistic infection. Outcomes were generally favorable after appropriate and timely treatment.

Acknowledgments
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References

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