Mycobacterium haemophilum in Immunocompromised Patients

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Mycobacterium haemophilum, a recently described pathogen, can cause an array of symptoms in immunocompromised patients. To date, 90 patients with this infection have been described worldwide. We report our institution’s experience with 23 patients who were treated from 1990 through 2000. Fourteen patients had undergone bone marrow transplantation, 5 were infected with human immunodeficiency virus, 3 had hematologic malignancies, and 1 had no known underlying immunosuppression. Clinical syndromes on presentation included skin lesions alone in 13 patients, arthritis or osteomyelitis in 4 patients, and lung disease in 6 patients. Although patients with skin or joint involvement had favorable outcomes, 5 of 7 patients with lung infection died. Prolonged courses of multidrug therapy are required for treatment. A diagnosis of M. haemophilum infection must be considered for any immunocompromised patient for whom acid-fast bacilli are identified in a cutaneous, synovial fluid or respiratory sample or for whom granulomas are identified in any pathological specimen.

Mycobacterium haemophilum is an increasingly recognized pathogen in immunocompromised patients that causes cutaneous, synovial, and, less frequently, pulmonary infections. The bacterium was first identified in 1978 by Sompolinsky et al. [1] in Israel in a woman with Hodgkin’s disease who developed septic arthritis and skin lesions. Before its discovery, it may have accounted for acid-fast bacilli (AFB) smear–positive but culture-negative skin lesions found in patients who underwent renal transplantation [2, 3]. Since 1978, 90 patients who have been infected with this pathogen worldwide have been described in the medical literature, including 17 patients from Memorial Sloan-Kettering Cancer Center (MSKCC) who were described elsewhere in a series of small reports [4–13]. Most of these 90 patients were immunocompromised, frequency because of HIV infection [4–9, 13–28] or because they had undergone organ transplantation [9, 12, 29–37], and, less frequently, because of hematologic malignancies or chronic conditions that required prolonged immunosuppressive therapy [9, 12, 38, 39]. However, M. haemophilum also has been reported to cause lymphadenitis in children who are apparently immunocompetent [9, 16, 40–42], and more recently, it has been reported to cause disease in a handful of adults without evident immunosuppression [11, 43].

M. haemophilum is a fastidious organism that exhibits unique growth requirements and, therefore, it may be relatively underrecognized and underreported. The standard isolation techniques that are used for other mycobacteria are not adequate for the isolation of this organism, because M. haemophilum grows optimally at 30°C to 32°C, as opposed to 37°C, which is the optimum temperature for most other pathogenic mycobacteria. Also, media must be supplemented with compounds that contain iron, such as ferric ammonium citrate or hemin [44–46]. Like many other non-tuberculous mycobacteria, it does not respond to treatment with isoniazid or pyrazinamide, but it may respond to other medications that are used in the...
treatment of patients with atypical mycobacteria, including the quinolones, the macrolides, and the rifamycins [9, 47].

To date, 23 patients with a spectrum of illnesses secondary to M. haemophilum have been identified and treated at MSKCC. This report describes our experience with treatment of these patients from 1990 through 2000, which, to our knowledge, is the largest known group of patients with this infection from a single institution.

METHODS

MSKCC is a tertiary-care cancer center in New York City with 437 beds and ~19,000 discharges per year. Cases were identified by systematic review of mycobacteriology laboratory reports from 1990 through 2000. In the laboratory, clinical specimens were stained with the auramine acid-fast stain, and cultured on Middlebrook 7H11 agar plates with X-factor strips (Becton-Dickinson Microbiology Systems) and incubated at 30°C in an atmosphere of 10% CO₂ for 6 weeks. Isolates were identified by the presence of conventional growth and biochemical characteristics [9]. Initially, isolates were also analyzed by means of restriction fragment length polymorphism studies [48]. Antimicrobial susceptibility patterns were determined by use of a disk elution method [43].

Retrospective chart review was performed on all culture-proven cases and information was collected onto standardized data extraction forms. Immune function was assessed by quantifying subset populations of peripheral blood T cells, which were obtained by means of standard techniques for peripheral blood phenotyping at the immunology laboratory at MSKCC. The absolute number was calculated from the WBC count and the differential that was performed on the same day, according to the following formula: absolute number = [(number WBCs × percentage of lymphocytes) × percentage of lymphoid subset]. Immune function results that were obtained nearest to the time of the diagnosis of M. haemophilum were used.

RESULTS

Patients. Information regarding the 23 patients who had infection with M. haemophilum diagnosed during the 11-year study period is noted in table 1. The median patient age was 42 years (range, 24–62 years). Twelve patients were men. Fourteen patients had undergone allogeneic bone marrow transplantation (BMT). Five patients had advanced HIV infection and 3 patients had underlying hematologic malignancies (2 patients had lymphoma and 1 patient had multiple myeloma). The patient with multiple myeloma also had a history of severe rheumatoid arthritis for which she was receiving long-term corticosteroid therapy. One patient, who had a history of treated stage 1 breast cancer, was believed to be immunocompetent, with no immediate risk factors for immunosuppression. However, the patient’s HIV status was unknown and her immune function was not formally assessed.

Disease presentation. The initial presentation for 13 patients was exclusively cutaneous. Lesions were typically described as tender, erythematous papules or nodules that later became suppurative and began to ulcerate. Lesions were most frequently located on the extremities, followed by the chest, the back, and, less frequently, the face. Four patients presented with joint disease, bone disease, or both. Two of these patients also had concomitant skin lesions.

One patient’s condition (patient 13) progressed from a cutaneous presentation to pulmonary involvement. This 49-year-old woman had a history of acute myelogenous leukemia and BMT. Three months after she presented with skin lesions, although she was apparently responding well to orally administered therapy, the patient developed a right upper lobe nodular density. An open-lung biopsy yielded M. haemophilum.

Six patients presented with pulmonary manifestations of M. haemophilum. Four of these patients had undergone BMT, 1 patient had advanced AIDS, and 1 patient was immunocompetent. Radiographic findings included infiltrates (in 3 patients), nodular changes (in 2 patients) and cavitory lung disease (in 1 patient). This last patient (patient 15), a 32-year-old man with a history of myelodysplastic syndrome and BMT, presented with fever, cough, hemoptysis, and infiltrative lung lesions that cavitated. His clinical course rapidly deteriorated before a diagnostic procedure or appropriate therapy could be instituted.

Immune function. Assessment of immune function data was available for 22 of 23 patients. The single patient for whom data were unavailable had no evidence of underlying immunosuppression. Absolute CD4 cell count was used as the marker to assess underlying cell-mediated immunity. The median CD4 cell count of the 22 patients was 76 cells/μL (range, 2–431 cells/μL). In subset analysis, the median CD4 cell count according to underlying disease was as follows: for patients who had undergone BMT, 101 cells/μL (range, 2–431 cells/μL); for patients with AIDS, 29 cells/μL (range, 11–194 cells/μL); and for patients with hematologic malignancies, 42 cells/μL (range, 38–352 cells/μL). The median CD4 cell count according to disease presentation was as follows: for patients with initial cutaneous as the only disease, 156 cells/μL (range, 2–431 cells/μL); for patients with initial joint or bone disease, 385 cells/μL (range, 21–419 cells/μL); and for patients with initial lung disease, 18 cells/μL (range, 6–42 cells/μL).

Antimicrobial susceptibility. Susceptibility data for tested isolates are summarized in table 2. Sixteen isolates from 13 patients were available for analysis. All isolates were sensitive to amikacin, ciprofloxacin, and clarithromycin. The only isolate that was resistant to rifampin was from 1 postmortem culture of patient 2, whose initial isolate, which was recovered 10
Table 1. Summary of the characteristics, disease presentation, therapy, and outcomes for patients who were infected with *Mycobacterium haemophilum* and who presented to the Memorial Sloan-Kettering Cancer Center, New York City, from 1990 through 2000.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, years</th>
<th>Sex</th>
<th>Underlying disease or history</th>
<th>CD4 cell count, cells/µL (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Initial clinical presentation</th>
<th>Date of culture</th>
<th>Culture source</th>
<th>Antibiotic therapy (duration)</th>
<th>Outcome</th>
<th>Reference&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>27</td>
<td>M</td>
<td>AA, BMT</td>
<td>36 (34)</td>
<td>Pulmonary nodules</td>
<td>8/27/90</td>
<td>Sputum, BAL, OLBx</td>
<td>RIF, Eth, Amik, Cm (1.5 months)</td>
<td>Death</td>
<td>[4–10]</td>
</tr>
<tr>
<td>2</td>
<td>35</td>
<td>M</td>
<td>AIDS</td>
<td>11 (2)</td>
<td>Skin, pulmonary infiltrate</td>
<td>9/14/90</td>
<td>Skin, sputum&lt;sup&gt;c&lt;/sup&gt;</td>
<td>RIF, Eth, Cpfx, Amik, Dox, Em (10 months)</td>
<td>Death</td>
<td>[4–9]</td>
</tr>
<tr>
<td>3</td>
<td>37</td>
<td>M</td>
<td>AIDS</td>
<td>21 (4)</td>
<td>Skin, synovitis</td>
<td>9/17/90</td>
<td>Synovial fluid</td>
<td>RIF, Eth, Cpfx, Amik, Dox (15 months)</td>
<td>Cure</td>
<td>[4–9, 13]</td>
</tr>
<tr>
<td>4</td>
<td>30</td>
<td>F</td>
<td>APL, BMT</td>
<td>431 (45)</td>
<td>Skin</td>
<td>3/11/91</td>
<td>Skin biopsy</td>
<td>RIF, Eth, Cpfx, Clm, Dox (7 months)</td>
<td>Cure</td>
<td>[4–10]</td>
</tr>
<tr>
<td>5</td>
<td>58</td>
<td>M</td>
<td>Lymphoma</td>
<td>38 (10)</td>
<td>Skin</td>
<td>9/28/92</td>
<td>Skin aspirate</td>
<td>RIF, Eth, Cpfx, Clm (5 months)</td>
<td>Cure</td>
<td>[12]</td>
</tr>
<tr>
<td>6</td>
<td>29</td>
<td>F</td>
<td>AML, BMT</td>
<td>419 (22)</td>
<td>Synovitis</td>
<td>1/22/93</td>
<td>Cyst fluid</td>
<td>RIF, Cpfx, Clm (6 months)</td>
<td>Cure</td>
<td>[9, 10]</td>
</tr>
<tr>
<td>7</td>
<td>28</td>
<td>F</td>
<td>AML, BMT</td>
<td>101 (15)</td>
<td>Skin</td>
<td>3/15/93</td>
<td>Skin biopsy</td>
<td>RIF, Cpfx, Clm (11 months)</td>
<td>Cure</td>
<td>[9, 10, 12]</td>
</tr>
<tr>
<td>8</td>
<td>43</td>
<td>M</td>
<td>MDS, BMT</td>
<td>18 (10)</td>
<td>Pulmonary infiltrate</td>
<td>12/7/93</td>
<td>Lung biopsy</td>
<td>RIF, Eth, Cpfx, Clm, Amik (10 days)</td>
<td>Death</td>
<td>[9, 10]</td>
</tr>
<tr>
<td>9</td>
<td>29</td>
<td>F</td>
<td>AIDS</td>
<td>29 (7)</td>
<td>Skin</td>
<td>3/16/94</td>
<td>Skin biopsy</td>
<td>RIF, Cpfx, Clm, Dox (11 months)</td>
<td>Death&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>51</td>
<td>F</td>
<td>Multiple myeloma, RA</td>
<td>42 (12)</td>
<td>Skin</td>
<td>9/16/94</td>
<td>Skin biopsy, blood</td>
<td>RIF, Eth, Cpfx, Clm (15 months)</td>
<td>Cure</td>
<td>[12]</td>
</tr>
<tr>
<td>11</td>
<td>35</td>
<td>M</td>
<td>AIDS</td>
<td>385 (13)</td>
<td>Osteomyelitis</td>
<td>10/21/94</td>
<td>Bone biopsy</td>
<td>RIF, Cpfx, Clm (5 months)</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>24</td>
<td>M</td>
<td>AML, BMT</td>
<td>76 (17)</td>
<td>Skin</td>
<td>5/15/95</td>
<td>Skin biopsy</td>
<td>RIF, Cpfx, Clm (10 months)</td>
<td>Cure</td>
<td>[12]</td>
</tr>
<tr>
<td>13</td>
<td>49</td>
<td>F</td>
<td>AML, BMT</td>
<td>158 (17)</td>
<td>Skin</td>
<td>11/2/95</td>
<td>Skin biopsy, OLBx&lt;sup&gt;e&lt;/sup&gt;</td>
<td>RIF, Cpfx, Clm, Amik (23 months)</td>
<td>Cure</td>
<td>[12]</td>
</tr>
<tr>
<td>14</td>
<td>33</td>
<td>F</td>
<td>NHL, BMT</td>
<td>110 (40)</td>
<td>Skin</td>
<td>5/16/96</td>
<td>Skin biopsy</td>
<td>Cpfx, Clm (24 months)</td>
<td>Cure</td>
<td>[12]</td>
</tr>
<tr>
<td>15</td>
<td>32</td>
<td>M</td>
<td>MDS, BMT</td>
<td>42 (6)</td>
<td>Pulmonary infiltrate</td>
<td>12/5/96</td>
<td>Blood</td>
<td>None</td>
<td>Death</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>42</td>
<td>M</td>
<td>NHL, BMT</td>
<td>2 (1)</td>
<td>Skin</td>
<td>4/18/97</td>
<td>Skin biopsy</td>
<td>RIF, Cpfx, Clm, Dox (20 months)</td>
<td>Cure</td>
<td>[12]</td>
</tr>
<tr>
<td>17</td>
<td>49</td>
<td>F</td>
<td>AML, BMT</td>
<td>204 (14)</td>
<td>Skin</td>
<td>9/25/97</td>
<td>Skin biopsy</td>
<td>RIF, Cpfx, Clm (24 months)</td>
<td>Cure</td>
<td>[12]</td>
</tr>
<tr>
<td>18</td>
<td>46</td>
<td>M</td>
<td>CML, BMT</td>
<td>115 (11)</td>
<td>Skin</td>
<td>11/3/97</td>
<td>Skin biopsy</td>
<td>RIF, Cpfx, Clm (13 months)</td>
<td>Cure</td>
<td>[12]</td>
</tr>
<tr>
<td>19</td>
<td>56</td>
<td>F</td>
<td>Lymphoma</td>
<td>352 (47)</td>
<td>Skin</td>
<td>12/18/97</td>
<td>Skin biopsy</td>
<td>RIF, Cpfx, Clm (2 months)</td>
<td>Death&lt;sup&gt;f&lt;/sup&gt;</td>
<td>[12]</td>
</tr>
<tr>
<td>20</td>
<td>62</td>
<td>F</td>
<td>None known</td>
<td>Unknown</td>
<td>Pulmonary nodule</td>
<td>10/15/98</td>
<td>Lung biopsy</td>
<td>RIF, Eth (1.5 months)</td>
<td>Cure</td>
<td>[11]</td>
</tr>
<tr>
<td>21</td>
<td>42</td>
<td>M</td>
<td>CML, BMT</td>
<td>6 (3)</td>
<td>Pulmonary infiltrate</td>
<td>7/20/99</td>
<td>BAL</td>
<td>RIF, Eth, Cpfx, Clm, Amik (1 month)</td>
<td>Death</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>51</td>
<td>M</td>
<td>AIDS</td>
<td>184 (17)</td>
<td>Skin</td>
<td>7/6/99</td>
<td>Skin aspiration</td>
<td>Eth, Cpfx, Clm (14 months; ongoing)</td>
<td>Improving</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>47</td>
<td>F</td>
<td>AA, BMT</td>
<td>333 (22)</td>
<td>Synovitis, osteomyelitis</td>
<td>7/6/00</td>
<td>Synovial fluid</td>
<td>RIF, Cpfx, Clm, Dox (6 months; ongoing)</td>
<td>Improving</td>
<td></td>
</tr>
</tbody>
</table>

**NOTE.** AA, aplastic anemia; Amik, amikacin; APL, acute promyelocytic leukemia; BAL, bronchoalveolar lavage; BMT, allogenic bone marrow transplantation; Clm, clarithromycin; Cm, clindamycin; CML, chronic myelogenous leukemia; Cpfx, ciprofloxacin; Dox, doxycycline; Em, erythromycin Eth, ethambutol; MDS, myelodysplastic syndrome; NHL, non-Hodgkin's lymphoma; OLBx, open-lung biopsy; RA, rheumatoid arthritis; Rif, rifampin or rifabutin.

<sup>a</sup> The normal range for absolute CD4 cell count is 549–1481 cells/µL; the normal range for CD4 cell percentages is 36%–59%.

<sup>b</sup> This refers to previously published reports from Memorial Sloan-Kettering Cancer Center, New York City, regarding these patients. Most previously published reports present clinical data [4–11, 13], and one presents mostly histological data [12].

<sup>c</sup> Cultures of sputum samples were performed 8 months later, in May 1991, when the patient’s condition deteriorated.

<sup>d</sup> The patient’s death was due to complications from advanced AIDS infection. At the time of death, the patient’s condition (cutaneous infection due to *M. haemophilum*) was stable, and the results of follow-up cultures were negative.

<sup>e</sup> The patient developed a pulmonary infiltrate ~3 months after the appearance of skin lesions. An open-lung biopsy was performed on 11 January 1996.

<sup>f</sup> The patient died as a result of progressive lymphoma. At the time of death, the patient’s condition (cutaneous disease due to *M. haemophilum*) was improving.
months earlier, was sensitive to rifampin. More variable sensitivity to doxycycline was demonstrated, and sensitivity to streptomycin was only established for the higher concentration of the drug. Complete resistance to ethambutol, ethionamide, and isoniazid was observed among all tested isolates.

**Antimicrobial therapy.** Twenty-one of 23 patients received an appropriate antibiotic regimen that contained at least 2 drugs with high in vitro activity against *M. haemophilum*. Patient 15, who was described above, died before a diagnosis was made; therefore, appropriate treatment had not yet been administered. Patient 20, a 62-year-old woman with a history of treated breast cancer and no other underlying risk factors for immunosuppression, underwent an excisional biopsy of a right upper lobe lung nodule [11]. When pathology revealed AFB, she began receiving antituberculosis therapy, which included rifampin and ethambutol. After 6 weeks of treatment, her cultures yielded *M. haemophilum*. At this point, she had no further sequelae of her disease, and therapy was discontinued. Two patients in our group (patients 22 and 23) are still undergoing therapy.

The median duration of antibiotic therapy for all 17 patients who were treated for infection and who had a known outcome related to *M. haemophilum* was 10 months (range, 0–24 months). Of the total of 23 patients, 6 patients were not included in this analysis: 2 patients were still receiving treatment for *M. haemophilum* infection, 2 patients died while receiving treatment (likely as a result of their underlying disease), 1 patient was lost to follow-up, and 1 patient died before receiving any therapy. The median duration of antibiotic therapy according to disease presentation was as follows: for patients with initial cutaneous-only disease, 14 months (range, 5–24 months); for patients with initial joint or bone disease, 9.5 months (range, 6–15 months); and for patients with initial lung disease, 1.5 months (range, 10 days to 10 months).

**Patient outcomes.** Overall, 12 patients were cured of *M. haemophilum*, 2 patients were improving while they were still receiving therapy, 5 patients died of *M. haemophilum* infection, 2 patients died of causes that were secondary to progression of their underlying disease while they were still receiving therapy, and 1 patient was lost to follow-up. All 5 deaths attributable to *M. haemophilum* involved patients who developed lung disease. The only other patient with initial lung disease was immunocompetent and had presented with a solitary pulmonary nodule; she survived the infection. One other patient, patient 13, who is described elsewhere and above, developed *M. haemophilum* pneumonitis while being treated for cutaneous disease [12]. She improved after the addition of amikacin to her antibiotic regimen.

**DISCUSSION**

Immunocompromised patients with *M. haemophilum* infection may present with an array of signs and symptoms. At MSKCC, with its unique population of patients who have severe immunosuppression due to either BMT or AIDS, a range of opportunistic infections has been observed. Worldwide, the mycobacteria has been isolated from specimens of numerous sites, including skin (often from multiple sites), synovial fluid, bone, lung tissue, sputum, bronchoalveolar lavage fluid, lymph nodes, blood, and bone marrow [9]. The identification of the organism in specimens of these multiple sterile sites, especially blood, suggests hematogenous dissemination of the infection.

Cutaneous and subcutaneous manifestations are the most frequently reported presentation of the infection in the literature and in this series from MSKCC. Lesions tend to be erythematous papules or nodules that later become tender and suppurative, which culminate in painful draining ulcers. Less frequently, they present as cysts, scaly plaques, or focal panniculitis. Lesions typically occur on the extremities, frequently overlying the joints. This may be explained by the low optimal temperature growth requirements for *M. haemophilum* and, therefore, a predilection to grow on relatively cooler areas of the body [20]. Biopsy specimens of the skin tend to test positive for AFB. In histopathological tests, a mixed granulomatous and suppurative reaction is observed with the greatest frequency. The granulomas are usually poorly formed and have varying amounts of necrosis [12]. Septic arthritis and osteomyelitis are less common manifestations in immunocompromised patients, and when they do occur, skin disease may also be present.

Lower respiratory tract symptoms have proven to be rarer but deadlier manifestations of *M. haemophilum* infection. In this series, 6 of 23 patients initially presented with some evidence of lung disease. Five of these patients were immuno-

### Table 2. Antimicrobial susceptibility profile.

<table>
<thead>
<tr>
<th>Drug (concentration)</th>
<th>Sensitivity, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin (2 μg/mL)</td>
<td>100</td>
</tr>
<tr>
<td>Ciprofloxacin (2 μg/mL)</td>
<td>100</td>
</tr>
<tr>
<td>Clarithromycin (3 μg/mL)</td>
<td>100</td>
</tr>
<tr>
<td>Doxycycline (6 μg/mL)</td>
<td>50</td>
</tr>
<tr>
<td>Ethambutol (5 μg/mL)</td>
<td>0</td>
</tr>
<tr>
<td>Ethionamide (5 μg/mL)</td>
<td>0</td>
</tr>
<tr>
<td>Isoniazid (0.2 μg/mL)</td>
<td>0</td>
</tr>
<tr>
<td>Rifampin (1 μg/mL)</td>
<td>94*</td>
</tr>
<tr>
<td>Streptomycin (2 μg/mL)</td>
<td>0</td>
</tr>
<tr>
<td>Streptomycin (10 μg/mL)</td>
<td>100</td>
</tr>
</tbody>
</table>

**NOTE.** Sixteen isolates that were recovered from 13 patients were analyzed. Thirteen isolates that were recovered from 13 patients were from samples obtained at the time of the initial diagnosis. Three isolates were recovered from patient 2 from a postmortem specimen after the patient had undergone 10 months of treatment.

* All initial isolates were sensitive to rifampin; however, 1 of 3 isolates from the postmortem cultures of patient 2 demonstrated resistance.
compromised, and they died as a result of their pulmonary *M. haemophilum* infection. Results of histopathological tests indicated that most of the patients who we studied had characteristic, loosely formed granulomas with varying amounts of necrosis. One patient had *M. haemophilum* recovered from a sputum sample, and the results of testing of an open-lung biopsy sample had findings consistent with bronchiolitis obliterans organizing pneumonia. Only 3 other patients reported in the medical literature have presented with respiratory disease attributable to *M. haemophilum*. All 3 of these patients had upper respiratory tract symptoms and findings, and none died from pulmonary disease [8, 20].

Cell-mediated immunity appears to play a significant role in the evolution of *M. haemophilum* disease pathogenesis and outcome. This theory is supported by the marked degree of immunosuppression, reflected by absolute CD4 cell count, in the 5 patients who presented with and died of pulmonary infection, compared with the other patients, who had cutaneous, joint, or bone involvement, none of whom died of causes that were secondary to *M. haemophilum* infection. Improvement of immune function during the course of a patient’s disease also appears to facilitate recovery from infection [32]. Patient 13 in our series, who developed infiltrative lung disease while being treated for her cutaneous mycobacterial disease, did well with an intensification of therapy and also had an improvement in her immune function. These clinical observations are supported by laboratory work in murine models; immunocompetent mice that were injected with *M. haemophilum* did not develop disease, unlike mice that had been rendered immunosuppressed with steroids, who went on to develop cutaneous disease that resembles that seen in humans [49].

However, as immune function improves, patients may also be susceptible to an immune reconstitution syndrome. Widely reported in patients who are receiving highly active antiretroviral therapy (HAART) for HIV or AIDS, especially patients with mycobacterial infections, this phenomenon involves newly competent T cells that cause acute inflammatory reactions, especially in the face of a sudden immune stimulus [50, 51]. One of the patients (patient 22) most likely developed his *M. haemophilum* infection in this setting. This 51-year-old man with recently diagnosed AIDS and Burkitt’s lymphoma had just begun receiving HAART 2 months prior to the eruption of skin lesions that later were proven to be due to *M. haemophilum*. At the time of the cutaneous eruption, his immune function, by all parameters, was improving, with a decrease in his virus load and an increase in his absolute CD4 cell count. Presumably, his mycobacterial infection was subclinical until the commencement of HAART, at which time a full-blown inflammatory reaction took place, with the *M. haemophilum* acting as the immune stimulus. His antiretroviral therapy was continued, and his lesions are slowly improving with antibiotic therapy.

Another recent, potential example of an immune reconstitution syndrome was reported in Maryland [28]. This report describes a 51-year-old man with AIDS who had developed cutaneous *M. haemophilum* infection. He was treated with both antimycobacterial medications and potent antiretroviral therapy. After several months, his lesions regressed and his immune function improved. During a routine clinic visit, a tetanus vaccination was administered. Within 1 day of the injection, he noted cutaneous lesions on his extremities that were similar to those that he had previously experienced. Aspirates again tested positive for AFB, but this time, the culture results remained negative. He continued the same antimycobacterial medications, and within a few weeks, his lesions resolved. In this case, the tetanus vaccination was postulated to be the nonspecific immune stimulator.

*M. haemophilum* appears primarily to cause disease in the following 2 distinct groups of patients: immunocompromised adults with a previously described spectrum of disease and immunocompetent children with lymphadenitis. An emerging subset of immunocompromised patients to have *M. haemophilum* infection diagnosed is persons who have undergone BMT. Fourteen of the patients at MSKCC underwent bone marrow allograft. Only 2 other patients who have undergone some form of BMT have recently been described in the literature; both patients were from the same institution in Australia, and both had *M. haemophilum* central venous catheter infection [35]. Overall, of the 14 patients who had undergone BMT who were managed at MSKCC, 4 died of the infection, 9 were cured, and 1 is still undergoing therapy 6 months into the course of her disease.

The other primary risk group for *M. haemophilum* infection is immunocompetent children who present with cervical, submandibular, or perihilar lymphadenitis. Eighteen patients have been described, including 9 patients who had infections within a 1-year period who were reported from a single institution in Israel [9, 16, 40–42]. Surgical excision of the affected lymph nodes is considered to be the treatment of choice. Clinically, the lymphadenitis in these children may be indistinguishable from lymph node infections caused by *Mycobacterium tuberculosis*, *Mycobacterium avium*–complex, or *Mycobacterium scrofulaceum*. Moreover, many of these patients react positively to the purified protein derivative of *M. tuberculosis*, which makes the establishment of an early clinical diagnosis even more confusing [40–42].

Two immunocompetent adults have been reported to have contracted *M. haemophilum* infection, including patient 20 in our series [11]. The other was a patient who had undergone coronary artery bypass grafting [43]. Postoperatively, she developed classic cutaneous disease and responded well to several
months of single-drug therapy and surgical excision [43]. However, in both of these patients, immune function parameters were never formally tested. Before these cases, a report from Canada in 1974 suggested *M. haemophilum* infection in a cluster of 29 patients for whom a definitive diagnosis was not established. These patients, who had no known risk factors for immunodeficiency, presented with adenitis and typical skin lesions [52]. This series was described before the discovery of *M. haemophilum*, and the mycobacteria observed in the acid-fast stains were not placed on media that would support the growth of this fastidious organism.

Growth of *M. haemophilum* on culture requires media that contain ferric ions. A variety of culture methods have been described elsewhere [9, 44–46]. In our laboratory, a practical method involves inoculating a specimen onto a Middlebrook 7H11 agar plate (Becton-Dickinson) and then adding a X-factor strip that contains hemin to the surface of the agar, which is then incubated at 30°C. Satellite growth should form around the paper strip, usually in 7–10 days. However, media should be incubated at 30°C for at least 6 weeks, a temperature that is also required for growth of *Mycobacteria marinum* and *Mycobacteria ulcerans*, organisms that also cause cutaneous disease. After growth is observed, the organism usually exhibits properties that are biochemically inert in most of the tests that are used to help speciate mycobacteria. Therefore, the laboratory relies on growth characteristics and a specific HPLC pattern for identification. On microscopic observation, the organism is usually a short bacillus and may exhibit cording, similar to that observed with *M. tuberculosis*.

There are no current guidelines regarding antibiotic management of *M. haemophilum* in immunocompromised patients. Previous reviews have reported success with a wide variety of antibiotic regimens [9, 53, 54]. Currently, there are no standardized antimicrobial susceptibility tests for *M. haemophilum*. Furthermore, it is not clear how these in-vitro test results predict clinical response. However, on the basis of the results of susceptibility testing of our isolates and the clinical outcomes of our patients, we recommend a 3-drug regimen that contains a macrolide, a rifamycin, and a quinolone. For sicker patients, including those who present with pulmonary symptoms, we would administer these 3 drugs with amikacin and perhaps doxycycline as well. The duration and amount of therapy should be guided by the patient’s underlying disease presentation and degree of immunosuppression. However, as demonstrated in our patient population, treatment should extend for at least 12 months and perhaps for as long as 24 months. Clinicians should be cognizant of the prolonged effects of an immune reconstitution syndrome when treatment is initiated. Often, lesions may become worse and patients may become more systemically ill during the first few months of treatment before improvement occurs. It is important to recognize that this is not necessarily a failure of therapy. Patient 23 in our series, a 47-year-old woman who had undergone BMT and who developed *M. haemophilum* elbow osteomyelitis, progressed with significant inflammation in her joint during the first 3 months of therapy, which eventually resolved. Aspirations of joint fluid demonstrated persistent AFB 2 months into the course of therapy. However, these later specimens were culture negative, which supports the efficacy of the antibiotic treatment regimen.

Diagnosis of infection early in its course is as important as the correct selection of antimicrobial agents. Because *M. haemophilum* is a fastidious organism that requires special isolation techniques that are not used routinely in most mycobacteria laboratories, the clinician must suspect the organism in any immunocompromised patient with unexplained skin lesions, joint space infection, or pneumonia. This concern must then be conveyed to the laboratory. Currently at our institution, any specimen that is specifically requested by a clinician or any AFB-positive smear is automatically cultured for *M. haemophilum*. Furthermore, all specimens of synovial or joint fluid, cutaneous lesions, ulcers, superficial wounds, and abscesses, and all skin, lymph node, and lung biopsy specimens are cultured for *M. haemophilum*. Consideration of special culture techniques should also be given for immunocompromised patients whose routine culture specimens or previous biopsy specimens, especially if granulomatous, remain nondiagnostic.

Our experience at MSKCC and a review of the cases reported elsewhere indicate that many epidemiologic questions regarding the transmission of this organism remain. *M. haemophilum*, like most other mycobacteria, is seemingly ubiquitous in the environment. However, no environmental reservoir has yet been identified. Previous studies have attempted to identify common aquatic sources, but to no avail [8]. Other case reports have addressed the issue of nosocomial transmission, again without identifying a common source [10]. Large clusters of cases have been reported from New York City, the southwest United States, Israel, and Australia. Whether these clusters are due to a common environmental link or to underidentification in other locations is not known. Various molecular epidemiologic studies have identified different strains of the organism specific to both location and underlying patient disease, which suggests clonal clustering in these varied geographic regions [48, 55]. Despite these large gaps in our understanding of the organism, the clinical disease can be effectively managed with prompt diagnosis and institution of treatment with several agents that have likely activity against *M. haemophilum*, which remains a significant pathogen among immunocompromised patients.

References