Summary: A major cause of morbidity and mortality in patients with cancer is infection. Since the introduction of the Haemophilus influenzae type b (Hib) vaccine in the United States in the 1990s, invasive H influenzae infection has become less common. We report on 5 patients with cancer and invasive H influenzae infection. A literature review was also performed of the dominant Haemophilus subtype and the clinical features associated with the infection and concomitant cancer. Of the 17 cases found in the literature, 7 had hematological malignancies and 1 case each had thymoma, schwannoma, teratoma, and pancreatic, Merkel cell, pharyngeal, laryngeal, and rectal carcinomas. Two cases occurred with AIDS and Kaposi sarcoma. Pneumonia with bacteremia was seen in 8 cases, whereas pleuritis, neck cellulitis, septic arthritis, meningitis, and mediastinitis were diagnosed in the others. No focus of infection was identified in 2 cases. Nontypable H influenzae (NTHi) occurred in 4 cases, and Hib was isolated in 2 cases; serotyping was not reported in the others. Leukocytosis occurred in 7 cases and lymphopenia in 3; no cases presented with neutropenia. Four isolates were positive for β-lactamase. Susceptibility data were unavailable in 5 case patients. Among serotyped cases, 67% were of the NTHi strain — a finding consistent with the change in the epidemiology of H influenzae since the introduction of the Hib vaccine.

Introduction

Haemophilus influenzae is a gram-negative coccobacillus that, when infecting humans, can manifest as bacteremia, meningitis, epiglottitis, cellulitis, and septic arthritis.1-4 It can be classified as typable H influenzae (encapsulated) or nontypable H influenzae (NTHi; unencapsulated). Encapsulated strains are further classified into 6 serotypes (a–f) based on the antigenic structure of the capsular polysaccharide, a critical virulence factor that mediates invasion of the bloodstream, thereby causing bacteremia.

H influenzae type b (Hib) is the most virulent organism of all 6 serotypes; however, due to the widespread childhood immunization program in the 1990s, the distribution of capsular serotypes in H influenzae disease shifted in the United States.1,5 H influenzae type f has been reported as the most frequent non–Hib capsulated strain.5-9 NTHi is also considered to be a significant cause of invasive H influenzae infection.5-12

Several risk factors exist for invasive H influenzae infections, including malignant neoplasms, asplenia, agammaglobulinemia, alcohol use disorder, AIDS, chronic pulmonary diseases, long-term steroid use, and undergoing chemotherapy, radiotherapy, or stem cell transplantation.2-4,6,11,13,14

Because malignancy is a risk factor for such infection, we report on our experience with H influenzae bacteremia since 2000 in our patients with cancer, including both solid and hematological malignancies, and their association with other comorbidities. A review of the literature was also performed to analyze specific risk factors, varied clinical presentations, outcomes, and antibiotic resistance patterns in relation to the cancer setting. To the best of our knowledge, no study after 1990 has assessed H influenzae infections in patients with cancer.

Case Reports

We reviewed the records of patients with documented invasive H influenzae infections seen at the H. Lee Moffitt Cancer Center & Research Institute in Tampa, Florida, between 2000 and 2015. The study population was identified from body fluids that were positive for H influenzae, the cultures of which were obtained from the microbiology laboratory during the same period of time. Patient records were reviewed for age, sex, clinical presentation, cancer diagnosis, underlying risk factors, comorbidities, previous hospitalization due to infection, medication use, presence or absence of neutropenia, procalcitonin levels, and antibiotic regimen. In addition, data regarding length of hospital stay and outcomes were reviewed.

Identification of the microorganisms was performed using standard microbiological methods.
Organisms suspected of being *H influenzae* were identified using the Rapid NH System (Thermo Fisher Scientific, Lenexa, KS). Antimicrobial susceptibilities were performed using standard Kirby-Bauer disk diffusion antibiotic sensitivity testing. *H influenzae* subtyping was not performed unless specifically ordered by the patient’s treating physician. This procedure has remained consistent at Moffitt Cancer Center since 2000.

From this retrospective search at Moffitt Cancer Center, 5 patients with *H influenzae* bacteremia were identified.

**Case 1**
A 63-year-old white man with a history of multiple myeloma (MM) complicated by stage 2 chronic kidney disease, immunoglobulin D γ monoclonal gammopathy, and anemia presented with fever and shortness of breath. He was being treated with pomalidomide and had been taking oral dexamethasone for 1 year. His medical history was significant for diabetes mellitus, hypertension, congestive heart failure, osteoarthritis, deep venous thrombosis, and pulmonary embolism, which required an inferior vena cava filter so he was placed on chronic anticoagulation. He was repeatedly hospitalized for right lower extremity cellulitis complicated by group G streptococci bacteremia. He was treated with vancomycin, clindamycin, and posaconazole for left lower-extremity cellulitis where a superficial wound culture isolated methicillin-resistant *Staphylococcus aureus* (MRSA) and *Mucor* species.

On presentation to the emergency department, he was febrile with a temperature of 100.5 °F. He reported recent exposure to his grandchildren who were having flulike symptoms. His white blood cell (WBC) count was 81,600/µL, and his absolute lymphocyte count was 1,000/µL — presumably secondary to long-term steroid use — and his procalcitonin level was 0.76 mg/dL. Screening cultures were positive for MRSA and vancomycin-resistant *Enterococcus faecium*. Findings on a respiratory viral panel and polymerase chain reaction was positive for *Rhinovirus*.

Lower-extremity Doppler ultrasonography revealed left popliteal deep venous thrombosis. Chest radiography showed new left lower lobe infiltrates as compared with findings on chest radiography obtained on a previous visit. Computed tomography (CT) of the chest revealed bilateral scattered infiltrates.

The patient was started on broad-spectrum antibiotics, including vancomycin and piperacillin/tazobactam, as well as posaconazole. On hospitalization day 2, both blood and sputum cultures demonstrated *H influenzae* positive for β-lactamase. Intravenous vancomycin and piperacillin/tazobactam were later discontinued and oral minocycline was started following the culture sensitivity results.

The patient’s condition significantly improved while on treatment, and he was discharged after 7 days in the hospital. He completed 2 weeks of oral minocycline, prophylactic oral levofloxacin, posaconazole, sulfamethoxazole/trimethoprim, and acyclovir. He continues follow-up visits at Moffitt Cancer Center for treatment of MM.

**Case 2**
A 51-year-old white man presented with fever, productive cough, and sinus congestion. He also complained of lower back and left flank pain with increased urinary frequency, nausea, and vomiting. His past medical history was significant for stage 3A κ-light chain MM, which was diagnosed 8 years from his current presentation.

He underwent autologous stem cell transplantation 4 years after being diagnosed with MM; however, because of the progression of his disease, the patient was treated with cyclophosphamide and high-dose prednisone. After his disease continued to progress, he was given lenalidomide.

He presented to the Blood and Marrow Transplant Outpatient Transplant clinic at Moffitt Cancer Center for scheduled treatment with dexamethasone pulse therapy but complained of a 3-day history of fever (103 °F). His WBC count was 36,800/µL (lymphocytopenia), absolute lymphocyte count was 500/µL, ionized calcium level was elevated at 10.6 mg/dL, and his total protein level was 10.8 g/dL. He did not have neutropenia. The patient declined hospitalization. Blood and urine cultures were collected. He was then started on daily oral levofloxacin.

On the third day following his visit, he returned to the outpatient clinic because the blood cultures were positive for gram-variable cocci. He was started on intravenous ceftriaxone 2 g daily and a single intravenous dose of daptomycin. Urine cultures grew fewer than 10,000/mL α-hemolytic streptococci. Blood cultures subsequently grew *H influenzae*.

Based on the culture and sensitivity results, the patient continued to receive intravenous ceftriaxone for 2 weeks. The patient again declined hospitalization, so he received home care for the intravenous antibiotics. Repeat blood cultures obtained 48 hours after the initial positive blood cultures remained sterile.

**Case 3**
A 73-year-old white man was hospitalized for left lower lobe pneumonia and sepsis after presenting to Moffitt Cancer Center with fever, cough, and rhinorrhea. His past medical history was significant for chronic lymphocytic leukemia (CLL), which was diagnosed 5 years prior to his presentation, as well as hypogammaglobulinemia, longstanding diabetes mellitus, and coronary artery disease, resulting in multiple previous hospitalizations. His history was also significant for recurrent
sinusitis and pneumonias that required 3 hospitalizations in a 2-year period. His most recent hospitalization occurred secondary to *Enterococcus* bacteremia 2 months prior to his presentation.

Upon his presentation to our institution, his temperature was 101.0 °F. His WBC count was 346,200/µL with bands on differential. CT of the chest demonstrated left lower lobe lung consolidation with pleural effusion (Fig). A right middle lobe nodule was cultured, but the findings were negative on biopsy. The histopathology was consistent with CLL. Blood and sputum cultures were obtained, and he was discharged home on oral levofloxacin.

However, he was hospitalized the following day after results from the blood cultures were positive for gram-negative coccobacilli. The patient was started on intravenous meropenem and was given a single dose of intravenous tobramycin pending culture identification and sensitivity results.

The blood and sputum cultures grew *H influenzae* negative for β-lactamase. The patient’s antibiotic treatment was switched to daily intravenous levofloxacin 750 mg following the sensitivity results, and he was discharged on oral levofloxacin after being hospitalized for 3 days. In total, he received 10 days of treatment.

Results were negative from follow-up cultures obtained 24 hours after the initial blood cultures. Follow-up CT of the chest showed significant improvement in the left lower lobe and a stable right middle lobe nodule.

**Case 4**
A 59-year-old white woman with a history of breast cancer and stage IV colorectal cancer was admitted from the clinic for hypotension and leukocytosis. She had recently established care at Moffitt Cancer Center after completing irinotecan and cetuximab at another facility for the treatment of colorectal cancer.

Despite this treatment, her disease had progressed and metastasized to her liver. Chemoembolization was considered, but she was deemed to be a poor candidate. Her carcinoembryonic antigen level increased from 53.6 to 78.5 ng/mL within 3 months, and her bilirubin level increased to 19 mg/dL requiring percutaneous drain placement.

Upon admission, she denied any upper respiratory symptoms or urinary complaints. She received volume resuscitation and pancytopenia was obtained prior to her receiving empirical therapy with intravenous ampicillin/sulbactam. Blood cultures were positive for *H influenzae* and *Streptococcus anginosus*. *Klebsiella oxytoca* and *S viridans* grew in the biliary fluid culture. Her hemodynamic status and WBC count improved during hospitalization. Based on sensitivity results, she was placed on oral levofloxacin 750 mg daily and completed a 2-week course of treatment.

**Case 5**
A 63-year-old white man presented to Moffitt Cancer Center in mild respiratory distress. He was post-CLL after a matched, unrelated donor stem cell transplant 2 years ago and also had a history of hypertension and chronic kidney disease. He was currently receiving prophylactic tacrolimus and sirolimus to prevent graft-vs-host disease, oral atovaquone as prophylaxis for pneumocystis pneumonia, and oral acyclovir for viral prophylaxis.

Chest radiography revealed right perihilar and right-base opacities. Blood cultures were obtained, and he was sent home with oral levofloxacin 750 mg after receiving 1 dose of intravenous ceftriaxone. However, he was asked to return to Moffitt Cancer Center because the blood cultures obtained were positive for gram-negative rods.

At the time of his admission, his respiratory condition deteriorated and he required intubation after he failed a trial of bilevel positive airway pressure and became hypoxic (oxygen saturation level of 63%). His temperature was 100.4 °F. Laboratory studies were obtained and were significant for leukocytosis (287,000/µL), monocytopsis, a blood urea nitrogen level of 34 mg/dL, a creatinine level of 1.3 mg/dL, and mildly elevated transaminases.

Imaging was performed, the results of which showed enlarging perihilar opacities and increasing bilateral, patchy airway disease suggestive of pneumonia. The patient was treated with 1 dose of tobramycin and meropenem.

Blood cultures grew *H influenzae* positive for β-lactamase. He was continued on daily treatment with intravenous ceftriaxone 2 g and oral levofloxacin 750 mg. He died on hospitalization day 5 due to multi-organ failure.
**Literature Review**

We performed an English-language literature review of cases in the United States of *H influenzae* infection among patients with cancer published between January 1, 1990, and December 31, 2015. A total of 129 articles were discovered. However, to be eligible for our review, patients had to be infected with *H influenzae* (typable and NTHi); be older than 18 years; be diagnosed with cancer (hematological and solid cancers); or have an infection that was the cause of the cancer. Based on these criteria, we identified 9 of the original 129 articles for inclusion in this review.4,12,15-20

In the studies reviewed, the age of the case patients ranged from 30 to 77 years; their mean age was 63.1 years (Table).4,12,15-20 Eleven men and 6 women made up the cases. Seven patients had hematological malignancies: 3 had MM, 3 had CLL, and 1 had lymphoma. One case patient each had pancreatic carcinoma, metastatic Merkel cell carcinoma (a neuroendocrine tumor of the skin), pharyngeal carcinoma, thymoma (resected 2 years prior to *H influenzae* infection), laryngeal cancer, recurrent rectal cancer, schwannoma (cranial nerve IX/X), and ruptured mediastinal mature cystic teratoma. Of the 2 patients with AIDS and Kaposi sarcoma, 1 had involvement of the lower extremity and 1 had right-ear involvement.

No data were found on the temperature and WBC count in 4 patients (cases 7–9 and 17). Two patients (cases 12 and 14) were afebrile on presentation. With the exception of 1 patient (case 6) whose temperature was 100.0 °F, all other patients presented with a temperature higher than 100.4 °F. None of the case patients had neutropenia.4,12,15-20 Seven patients had leukocytosis and 3 had lymphopenia.

Four patients (cases 7, 8, 13, and 14) were infected with NTHi, a fact documented after serotyping. Hib was isolated in 2 patients (cases 9 and 16). In the

### Table. — Summary of the Literature Review for Invasive *Haemophilus influenzae* Infections in Patients With Cancer

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age, y</th>
<th>Sex</th>
<th>Malignancy</th>
<th>Fever (°F)</th>
<th>WBC Study</th>
<th>Culture</th>
<th>Sensitivity Data</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>63</td>
<td>M</td>
<td>MM</td>
<td>100.5</td>
<td>Lymphopenia</td>
<td><em>H influenzae</em></td>
<td>Positive for β-lactamase</td>
<td>Pneumonia</td>
</tr>
<tr>
<td>2</td>
<td>51</td>
<td>M</td>
<td>MM</td>
<td>103.0</td>
<td>Lymphopenia</td>
<td><em>H influenzae</em></td>
<td>Pansensitive</td>
<td>URI</td>
</tr>
<tr>
<td>3</td>
<td>73</td>
<td>M</td>
<td>CLL</td>
<td>101.0</td>
<td>Leukocytosis</td>
<td><em>H influenzae</em></td>
<td>Pansensitive</td>
<td>Pneumonia</td>
</tr>
<tr>
<td>4</td>
<td>59</td>
<td>W</td>
<td>Rectal carcinoma</td>
<td>100.6</td>
<td>Leukocytosis</td>
<td><em>H influenzae</em></td>
<td>Positive for β-lactamase</td>
<td>Sepsis</td>
</tr>
<tr>
<td>5</td>
<td>63</td>
<td>M</td>
<td>CLL</td>
<td>100.4</td>
<td>Leukocytosis</td>
<td><em>H influenzae</em></td>
<td>Positive for β-lactamase</td>
<td>Pneumonia</td>
</tr>
<tr>
<td>6</td>
<td>73</td>
<td>M</td>
<td>Metastatic Merkel cell carcinoma</td>
<td>100.0</td>
<td>Low WBC count</td>
<td><em>H influenzae</em></td>
<td>Pansensitive</td>
<td>Pneumonia</td>
</tr>
<tr>
<td>7</td>
<td>77</td>
<td>W</td>
<td>Pancreatic carcinoma</td>
<td>—</td>
<td>—</td>
<td>NTHi</td>
<td>—</td>
<td>Pneumonia</td>
</tr>
<tr>
<td>8</td>
<td>65</td>
<td>M</td>
<td>Pharyngeal cancer</td>
<td>—</td>
<td>—</td>
<td>NTHi</td>
<td>—</td>
<td>Pleuritis</td>
</tr>
<tr>
<td>9</td>
<td>77</td>
<td>W</td>
<td>Lymphoma</td>
<td>—</td>
<td>—</td>
<td><em>H influenzae</em> type B</td>
<td>—</td>
<td>Pneumonia</td>
</tr>
<tr>
<td>10</td>
<td>75</td>
<td>M</td>
<td>KS (lower extremity)</td>
<td>101.3</td>
<td>Leukocytosis</td>
<td><em>H influenzae</em></td>
<td>—</td>
<td>No source found</td>
</tr>
<tr>
<td>11</td>
<td>67</td>
<td>M</td>
<td>KS (right ear)</td>
<td>104.9</td>
<td>Leukocytosis</td>
<td><em>H influenzae</em></td>
<td>Positive for β-lactamase</td>
<td>Right neck cellulitis</td>
</tr>
<tr>
<td>12</td>
<td>70</td>
<td>W</td>
<td>Thymoma</td>
<td>—</td>
<td>Lymphopenia</td>
<td><em>H influenzae</em></td>
<td>Pansensitive</td>
<td>Pneumonia</td>
</tr>
<tr>
<td>13</td>
<td>57</td>
<td>M</td>
<td>Laryngeal cancer</td>
<td>101.8</td>
<td>Leukocytosis</td>
<td>NTHi</td>
<td>Pansensitive</td>
<td>Septic arthritis</td>
</tr>
<tr>
<td>14</td>
<td>71</td>
<td>M</td>
<td>CLL</td>
<td>—</td>
<td>Leukocytosis</td>
<td>NTHi</td>
<td>Pansensitive</td>
<td>PJI</td>
</tr>
<tr>
<td>15</td>
<td>43</td>
<td>W</td>
<td>MM</td>
<td>103.0</td>
<td>No neutropenia</td>
<td><em>H influenzae</em></td>
<td>Pansensitive</td>
<td>Septic arthritis (right knee)</td>
</tr>
<tr>
<td>16</td>
<td>30</td>
<td>W</td>
<td>Schwannoma (cranial nerve IX, X)</td>
<td>101.8</td>
<td>No neutropenia</td>
<td>CSF</td>
<td><em>H influenzae</em> type B</td>
<td>Pansensitive</td>
</tr>
<tr>
<td>17</td>
<td>58</td>
<td>M</td>
<td>Teratoma (mediastinum)</td>
<td>—</td>
<td>—</td>
<td>Mediastinal tissue</td>
<td><em>H influenzae</em></td>
<td>—</td>
</tr>
</tbody>
</table>

CLL = chronic lymphocytic leukemia, CSF = cerebrospinal fluid, KS = Kaposi sarcoma, M = man, MM = multiple myeloma, NTHi = nontypable *H influenzae*, PJI = prosthetic joint infection, URI = upper respiratory infection, W = woman, WBC = white blood cell.

From references 4, 12, and 15 to 20.
remaining case patients, no *H influenzae* serotyping data were noted. No susceptibility data were available for 5 patients (cases 7–10 and 17). In 4 patients (cases 1, 4, 5, and 11), bacteria positive for β-lactamase were isolated. In the remaining case patients, the bacteria cultures were negative for β-lactamase.

Eight case patients were diagnosed with pneumonia with bacteremia. One case report (case 14) documents a possible chest infection complicated by bacteremia and hematogenous dissemination to the joint. No focus of infection was noted in 2 patients (cases 4 and 10). Pleuritis, right-sided neck cellulitis, septic arthritis, postsurgical bacterial meningitis, and mediastinitis after teratoma rupture were diagnosed in the remaining patients.

*H influenzae* infection resolved in all but 3 case patients (cases 5, 7, and 10). One patient (case 10) was unable to be extubated after undergoing abdominal aortic bypass surgery. As the condition of the patient worsened with persistent acidosis, the patient died after 41 days of hospitalization, which is when support measures were withdrawn following consent given by the patient’s family.

**Discussion**

Infections remain a major cause of morbidity and mortality among patients with cancer, and this is especially true after systemic chemotherapy–induced neutropenia. Traditional causative organisms include gram-negative bacilli such as *Enterobacteriaceae* and *Pseudomonas*. However, gram-positive bacteremia is experiencing resurgence due to the frequent use of fluoroquinolone prophylaxis for prolonged neutropenia.

In the last 30 years since the introduction of the Hib vaccination to the United States, and with many countries now adopting widespread immunization programs, a considerable change has occurred in the epidemiology of *H influenzae* infections. For example, NTHi is emerging as an important cause of invasive *Haemophilus bilus* infections. Although 65% of the cases described in the present review were not serotyped, 6 cases for which this information was available revealed that 4 cases (67%) were NTHi and 2 (33%) were Hib. Thus, our findings reiterate the importance of NTHi as a cause of infection.

In the last 30 years since the introduction of the Hib vaccination to the United States, and with many countries now adopting widespread immunization programs, a considerable change has occurred in the epidemiology of *H influenzae* infections. For example, NTHi is emerging as an important cause of invasive *Haemophilus* infections. Although 65% of the cases described in the present review were not serotyped, 6 cases for which this information was available revealed that 4 cases (67%) were NTHi and 2 (33%) were Hib. Thus, our findings reiterate the importance of NTHi as a cause of *H influenzae* bacteremia. Laboratory personnel should be encouraged to further serotype *Haemophilus* species so that we can begin to recognize different types of infections associated with the subtypes that may later help us determine the immunity needed against them.

It is also worth noting that *H influenzae* infections are common at both extremes of age. In addition to the changes in the serotype distribution of *H influenzae* infections, widespread childhood immunization has shifted the trend of infection toward elderly persons with comorbidities. Common factors include cancers and other immunocompromised states, and this is especially true where humoral immunity is compromised. MM is the major malignancy among them. Chronic kidney disease is also a condition associated with an increased risk of invasive *Haemophilus* infection.

Thus, advocating for immunization in elderly patients could influence the prevalence of invasive Hib in this age group. Because NTHi is becoming the predominant strain of *H influenzae* causing infections in humans, new vaccines are needed that do not target the capsular polysaccharide alone. One-tenth of *Haemophilus* species live in the human respiratory tract, and at least 8 different species colonize the nasopharyngeal cavity, so new vaccines should focus on nasopharyngeal carriage. A licensed, 10-valent pneumococcal vaccine conjugated to the immunogenic outer membrane protein D of *H influenzae* could potentially prevent invasive disease.

Although upper respiratory infection was the most common presentation in our cases (> 50%), other organ systems have also been involved. In other published reports, the primary focus of infection is not always recognized. Fulminant sepsis with *H influenzae* is more common in those with immunodeficiency and in those with asplenia. In addition, direct mucosal disruption can also cause invasive disease.

Patterns of antibiotic susceptibility for *H influenzae* differ and depend on geographical location. Most strains are susceptible to ampicillin, but resistance to ampicillin continues to be reported, as was documented in this review. The most common mechanism for this is the prevalence of strains producing β-lactamase, although alteration of penicillin-binding proteins has also been described. Strains producing β-lactamase were isolated in 4 cases described in our study.

**Conclusions**

*Haemophilus influenzae* bacteremia is not a rapidly fatal process when compared with bacteremia caused by other gram-negative bacilli. In our study, patients without severe medical comorbidities or widespread metastatic malignancies remained in the hospital for less than 1 week and appeared to completely recover from the infection. Of the 17 cases found in the literature, 14 were reported to have a full resolution of their infection after prompt treatment; the 3 other patients were elderly (≥ 63 years). Because widespread childhood immunization has shifted the trend of infections in the United States toward elderly patients with comorbidities, and because the case fatality rate of these invasive infections increases with age, it is important that we develop preventive and treatment options designed for the elderly population.
References