Infectious Complications in Adult Patients with Hemophagocytic Lymphohistiocytosis: A Single Center Experience

Joanna K. Nelson, MD; Beth Martin, MD; Eric Lau, DO; Dora Ho, MD, PhD
(1) Division of Infectious Diseases & Geographic Medicine, (2) Division of Hematology, Department of Medicine, Stanford University School of Medicine, Stanford, CA; 3) Department of Medicine, Santa Clara Valley Medical Center, San Jose, CA, USA

Background
- Hemophagocytic lymphohistiocytosis (HLH) is a rare hematologic disorder which is characterized by excessive immune activation. In adults, it is typically secondary to an underlying process such as autoimmune disease, infection, or malignancy.
- Guidelines based on expert opinion suggest prophylaxis with antiviral, antibacterial, and/or anti-fungal agents for patients undergoing treatment for HLH.
- The incidence of infectious complications in patients with HLH is not known.

Objectives/Aims
- We aimed to study the scope of infection in patients with HLH to help determine the best strategy for antimicrobial prophylaxis.

Methods
- We performed a retrospective chart review of 56 adult patients who fulfilled clinical diagnostic criteria for HLH treated at Stanford University Hospital between 2012-2018.
- Infections diagnosed from 1 month prior to 6 months after a diagnosis of HLH were reviewed. Infection related variables were collected, and descriptive statistics were performed.

Limitations
- Majority of patients reviewed received some form of prophylaxis, which likely impacted the number and types of infection that developed.
- This was a single center study.

Results
- A total of 94 infections were found in 33 of 57 episodes (58%) of HLH among 56 patients.
- 27 infections were diagnosed prior to HLH diagnosis and 67 infections were diagnosed after the diagnosis of HLH.
- The majority of infections pre-HLH diagnosis were viral, and most due to EBV (n=16). 13 of these had concomitant EBV-associated malignancies. Infection was thought to be a significant trigger of HLH in 5 cases: EBV (3), MAC (1), Histoplasma (1).
- Types of infections that occurred after the diagnosis of HLH:
  - **Bacterial**: n=46 (occurred in 44% of HLH episodes)
    - Bacteremia (20), pneumonia (7), soft tissue (6), intraabdominal (5), urinary tract infection (6), other (2).
  - **Fungal**: n=11 (19% of HLH episodes):
    - 9 proven and 2 possible (see Table)
  - **Viral**: n=10 (16% of HLH episodes):
    - CMV (4), HHV6 viremia (3), H1N1 influenza (1), BK viruria (1), RSV (1)

<table>
<thead>
<tr>
<th>Proven Fungal Infections</th>
<th>Diagnosis</th>
<th>Microbiology</th>
<th>Time of dx</th>
<th>Cause of HLH</th>
<th>Days ANC &lt;500</th>
<th>ANC at dx</th>
<th>Prophylaxis</th>
<th>Outcome: IFI related mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fungemia</td>
<td>Rhodotorula mucilaginosa</td>
<td>70</td>
<td>T-cell lymphoma</td>
<td>10</td>
<td>1340</td>
<td>none</td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td>Fungemia and retinitis</td>
<td>Candida albicans</td>
<td>44</td>
<td>T-cell lymphoma</td>
<td>17</td>
<td>0</td>
<td>posaconazole</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>Fungemia</td>
<td>Candida glabrata</td>
<td>115</td>
<td>T-cell lymphoma</td>
<td>26</td>
<td>1660</td>
<td>posaconazole</td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td>Fungemia</td>
<td>Candida glabrata</td>
<td>20</td>
<td>MAC</td>
<td>11</td>
<td>0</td>
<td>posaconazole</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>Pulmonary and mediastinal mucormycosis</td>
<td>Rhizopus</td>
<td>28</td>
<td>T-cell lymphoma</td>
<td>20</td>
<td>1000</td>
<td>posaconazole</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>Orbital mucormycosis</td>
<td>Rhizopus</td>
<td>25</td>
<td>MM/MDS</td>
<td>0</td>
<td>8590</td>
<td>none</td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td>Pulmonary and CNS Aspergillus fumigatus</td>
<td>15</td>
<td>DLBCL</td>
<td>14</td>
<td>600</td>
<td>fluconazole</td>
<td>no</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary mucormycosis</td>
<td>Syncephalastrum</td>
<td>65*</td>
<td>RA</td>
<td>n/a</td>
<td>0</td>
<td>caspofungin</td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td>Disseminated mucormycosis</td>
<td>Rhizopus</td>
<td>12*</td>
<td>Stills dz</td>
<td>7</td>
<td>0</td>
<td>caspofungin</td>
<td>yes</td>
<td></td>
</tr>
</tbody>
</table>

* days after HLH diagnosis made
* diagnosed post-mortem

Conclusions
- Infectious complications of HLH are common, and likely result from a combination of host immune factors related to underlying disease and induced by immunosuppressive chemotherapy.
- Most noteworthy is the high incidence of fungal infections which supports the use of antifungal prophylaxis in this patient population.
- Even with prophylaxis, breakthrough fungal infections, including with opportunistic molds, is not uncommon.