Salmonella Lung Involvement in Patients With HIV Infection*

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**Study objective:** To determine the frequency, clinical features, and outcome of lung involvement in HIV-infected patients having nontyphoid strains of Salmonella bacteremia.

**Design:** A retrospective clinical study.

**Patients and setting:** We studied the records of all HIV-infected patients with Salmonella bacteremia diagnosed at a university tertiary hospital from January 1987 to December 1995.

**Results:** Lung involvement was found in 18 (35.3%) of 51 HIV-infected individuals with Salmonella bacteremia. Six of 18 (33.3%) were diagnosed as having definite Salmonella pulmonary infection by isolation of Salmonella from respiratory specimens, while probable Salmonella lung disease was considered in two patients who developed lung abscesses without the identification of any pathogen. Predisposing factors for focal disease, such as prior lung disease or Salmonella serotype, were equally prevalent regardless of the presence of Salmonella pulmonary involvement. Cavitary infiltrates or abscess formation were seen in five of the eight patients. With the exception of one patient coinfected with *Nocardia asteroides* who died 1 month later, all patients were cured with antibiotic treatment. Superinfection with other pulmonary pathogens (10 cases, 56%) was more frequent than Salmonella pneumonia; the most frequent alternative diagnosis was *Pneumocystis carinii* pneumonia (5 cases, 28%), pyogenic bacterial infection (17%), and tuberculosis (11%).

**Conclusions:** In HIV-infected patients with Salmonella bacteremia, lung involvement is frequent, although there were no significant factors to explain this association. Cavitary disease was the most common radiologic pattern, and focal lung disease due to Salmonella does not seem to be associated with a worse prognosis. Coinfection and superinfection with other respiratory pathogens are more common than isolated Salmonella lung disease, and therefore, additional diagnostic procedures must be considered in the evaluation of these patients.

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**Key words:** AIDS; HIV infection; Salmonella bacteremia; Salmonella pneumonia

**Abbreviations:** IVDU=IV drug user

Pleuropulmonary complications due to nontyphoid strains of Salmonella have been recognized and described in patients with underlying conditions such as malignancies, uremia, hypochlorhydria, and following gastrectomy.1,2 Despite the high rate of Salmonella bacteremia associated with HIV infection or with established AIDS,3 focal involvement due to these agents is rare, and Salmonella has been rarely cited as a significant respiratory pathogen in this population.4,5

Over the past years, we have seen several HIV-infected patients with respiratory symptoms during Salmonella bacteremia episodes. The aim of this study was to evaluate, by retrospective analysis, the presentation of Salmonella lung disease, along with the spectrum of pulmonary pathogens in HIV-infected patients with Salmonella bacteremia during a 9-year period from 1987 to 1995.

**Materials and Methods**

We reviewed the clinical charts of all HIV-infected patients with Salmonella bacteremia seen at the Infectious Disease Unit of Ramón y Cajal Hospital (Madrid, Spain), from January 1987 through December 1995, in search of all subjects with respiratory symptoms. The Infectious Disease Unit provides primary and specialized care to HIV-seropositive patients in a university hospital attending a population of about 500,000 persons. During
the study period, a total of 4,416 HIV-infected patients have received their regular clinical management at our unit. The risk factor for HIV infection was IV drug abuse in 66.7% of patients, homosexuality in 18.7%, heterosexual intercourse with HIV-infected individuals in 14.1%, and transfusion of blood or blood products in 0.5% of patients.

Information collected from the patient’s medical record included epidemiologic and clinical data, diagnostic procedures, radiologic patterns, response to treatment, and outcome. All patients with respiratory symptoms and evidence of radiographic infiltrates were studied to determine a causal agent. Confirmed or definite Salmonella pulmonary infection was defined in case of bacteremia and a positive culture for Salmonella obtained from sputum, BAL, or lung tissue; probable Salmonella lung disease included those cases with bacteremia and absence of Salmonella isolation from respiratory specimens, and non-Salmonella pulmonary disease was considered in patients with bacteremia but simultaneous isolation of other pathogens from respiratory samples.

We considered satisfactory clinical response in case of symptoms remission and radiographic improvement after treatment.

Continuous variables were compared using an unpaired Student’s t test. Categorical variables were compared using χ² with continuity correction where applicable. A p value<0.05 was considered to be statistically significant.

Results

Study Population

During the study period, we detected 51 episodes of Salmonella bacteremia in 43 male and 8 female HIV-infected patients, with a mean age of 30 years (range, 22 to 61 years). The risk factor for HIV infection could be identified in all cases: 40 patients (78%) were IV drug users (IVDUs), five (10%) were homosexual men, four (8%) were hemophiliacs, and two (4%) had been heterosexual partners of HIV-infected persons. Mean CD4 cell count was 70/mm³ (range, 5 to 465); however, in 12 patients, HIV infection was diagnosed at the time of Salmonella bacteremia. Although diarrhea was present in 19 of the patients, simultaneous recovery of Salmonella from stools occurred in only 2 cases. The most prevalent serotype isolated in blood cultures was Salmonella enteritidis (30 cases, 59%).

Respiratory symptoms together with abnormal chest radiographs were present in 18 patients (35.3%). Culture of respiratory specimens (spontaneous or induced sputum, BAL fluid) yielded an etiologic agent in 16 patients: nontyphoid Salmonella in 6 cases (2 of which were coinfected with Nocardia asteroides and Pneumocystis carinii, respectively), P carinii in 5, Mycobacterium tuberculosis in 2, Streptococcus pneumoniae in 2, and Haemophilus influenzae in 1 patient. Two cases were defined as probable Salmonella lung disease.

Confirmed Salmonella Pulmonary Infection

Six patients fulfilled the criteria for definite nontyphoid Salmonella pneumonia. All of them were men, with a mean age of 26 years, and the most frequent risk factor for HIV infection was IV drug abuse (five cases). The mean CD4 lymphocyte count was 78/mm³ (range, 42 to 132). Pulmonary tuberculosis in two patients, and P carinii pneumonia in one, had been diagnosed before the episode of Salmonella bacteremia. The main complaints were fever, cough, sputum production, and pleuritic pain. Diarrhea was observed only in one case. The mean duration of symptoms before diagnosis was 17 days (range, 7 to 30). Chest radiograph showed cavitory lesions in three cases and lobar infiltrates in two. Despite the presence of nontyphoid strains of Salmonella in sputum specimens of three patients, fibrobronchoscopy with BAL or percutaneous lung needle aspiration were performed to confirm the diagnosis. Empiric tuberculostatic treatment was started in one case with a lung abscess before a definitive diagnosis could be achieved.

As previously noted above, in two cases, a concomitant opportunistic disease was diagnosed. One patient underwent an open lung biopsy owing to the lack of response to antibiotic therapy and lung tissue culture yielded N asteroides along with S enteritidis, whereas in another patient with a cavitary infiltrate, staining of BAL fluid also revealed P carinii.

Blood cultures revealed S enteritidis in five patients and Salmonella typhimurium in one, the same serotypes isolated from pulmonary samples. Salmonella was recovered from the stool only in one patient. All strains were susceptible to ampicillin, trimethoprim-sulfamethoxazole, and quinolones. IV antibiotic treatment was started with cefotaxime, ampicillin, or cotrimoxazole in two cases each, and then switched to oral ciprofloxacin in two. All but one patient recovered after a mean duration of therapy of 21 days; this was the one with N asteroides coinfection, who died 1 month later. The six patients were followed up until death (median time, 615 days). Table 1 summarizes the clinical features of these cases, together with those previously reported.

Probable Salmonella Lung Disease

This category included two cases with Salmonella bacteremia and a lung abscess on the chest radiograph, in which a definite etiology was not found despite percutaneous lung needle aspiration.

The eight patients considered to have Salmonella lung disease, either definite or probable, had no differences regarding prior lung abnormalities or CD4+ cell count, as compared with the remaining 43 bacteremic patients without Salmonella lung disease (Table 2).
Nonsalmonella Lung Disease

In 10 patients, another pulmonary infection developed concurrently with Salmonella bacteremia. Overall, *P. carinii* represented the first cause of pneumonia in these patients, accounting for five (10%) of all bacteremic patients and 28% of those with respiratory complaints, followed by bacterial pneumonia with three cases (17%) and *M. tuberculosis* with two (11%). Most patients were IVDUs (7 cases), and the mean CD4 cell count was 50/mm$^3$ (range, 11 to 204). Chest radiographs showed bilateral interstitial infiltrate in five cases, thin-wall upper lobe cavities in one patient with *P. carinii* pneumonia, single unilateral lobar infiltrate in three cases (one with tuberculosis and two with bacterial pneumonia), and an upper nodular infiltrate with small areas of cavitation in one patient with tuberculosis.

**DISCUSSION**

Salmonella bacteremia occurs between 15 and 100 times more frequently in AIDS patients than in the general population.\(^3\),\(^6\) Defective cell-mediated immunity is believed to be the basis for the increased incidence of this agent.\(^6\)–\(^9\) Other possible mechanisms that account for this increased frequency of salmonellosis include impaired B-cell function, prior use of antibiotics, and a diminished gastric acidity.\(^7\),\(^8\) IV drug abuse, due to the possible self-injection of contaminated water, and geographic location may increase the incidence.\(^9\)–\(^8\) The study population showed a relative high proportion of heterosexual IVDU among the HIV-infected patients with Salmonella bacteremia. It could also reflect a group of low socioeconomic status predisposed to poor hygienic conditions, and therefore to the acquisition of Salmonella. Despite this, our incidence of salmonellosis among HIV-infected patients was low (1.1%), and similar to that previously described in geographic areas such as New Jersey.\(^10\),\(^11\)

Lung involvement due to nontyphoid strains of Salmonella was first recognized in patients with underlying conditions, such as malignancy, diabetes mellitus, corticosteroid therapy, or alcohol abuse.\(^1\) In these patients, it is frequent to find a history of prior lung abnormalities, acute onset of pulmonary disease, and a high mortality related to the presence of immunosuppression in elderly patients with underlying pulmonary diseases.\(^12\),\(^13\) Previous studies of Salmonella infection in HIV-positive patients have largely been limited to nonpulmonary infection,\(^14\),\(^15\) with only several case reports describing patients with cavitary infiltrates who recovered after antibiotic therapy.\(^16\)–\(^19\) There is an inherent bias because patients with necrotizing lung disease are more likely to undergo invasive diagnostic procedures. Nevertheless, five patients in our series had cavitary lesions. These cases, like ours, are characterized by an adequate response to medical treatment, and the overall mortality attributable to Salmonella pulmonary infection was considerably lower among HIV-

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**Table 1—Clinical Features of the Patients With Isolation of Nontyphoid Strains of Salmonella in Respiratory Samples**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age, yr/Sex</th>
<th>Risk Factor</th>
<th>CD4/mm$^3$</th>
<th>Chest Radiograph</th>
<th>Source</th>
<th>Organisms</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR</td>
<td>28/M</td>
<td>HS</td>
<td>132</td>
<td>Lung abscess</td>
<td>BAL, sputum</td>
<td><em>S. enteritidis</em></td>
<td>Survived</td>
</tr>
<tr>
<td>PR</td>
<td>29/M</td>
<td>IVDU</td>
<td>65</td>
<td>Lung abscess</td>
<td>PLNA</td>
<td><em>S. enteritidis</em></td>
<td>Survived</td>
</tr>
<tr>
<td>PR</td>
<td>29/M</td>
<td>IVDU</td>
<td>61</td>
<td>Lobar infiltrate</td>
<td>Sputum</td>
<td><em>S. typhimurium</em></td>
<td>Survived</td>
</tr>
<tr>
<td>PR</td>
<td>28/M</td>
<td>IVDU</td>
<td>42</td>
<td>Lobar infiltrate</td>
<td>BAL, sputum</td>
<td><em>S. enteritidis</em></td>
<td>Survived</td>
</tr>
<tr>
<td>PR</td>
<td>26/M</td>
<td>IVDU</td>
<td>38</td>
<td>Cavitary infiltrate</td>
<td>BAL</td>
<td><em>S. enteritidis</em> and <em>P. carinii</em></td>
<td>Survived</td>
</tr>
<tr>
<td>PR</td>
<td>30/M</td>
<td>IVDU</td>
<td>112</td>
<td>Upper nodular infiltrates</td>
<td>Lung tissue</td>
<td><em>S. enteritidis</em> and <em>N. asteroides</em></td>
<td>Died</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age, yr/Sex</th>
<th>Risk Factor</th>
<th>CD4/mm$^3$</th>
<th>Chest Radiograph</th>
<th>Source</th>
<th>Organisms</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>29/M</td>
<td>IVDU</td>
<td>80</td>
<td>Cavitary lesion</td>
<td>BAL, sputum</td>
<td><em>S. enteritidis</em></td>
<td>Survived</td>
</tr>
<tr>
<td>17</td>
<td>49/M</td>
<td>NR</td>
<td>1</td>
<td>Lung abscess</td>
<td>Sputum</td>
<td><em>S. enteritidis</em></td>
<td>Survived</td>
</tr>
<tr>
<td>18</td>
<td>28/M</td>
<td>IVDU</td>
<td>69</td>
<td>Cavitary lesions</td>
<td>BAL</td>
<td><em>S. typhimurium</em></td>
<td>Survived</td>
</tr>
<tr>
<td>19</td>
<td>40/M</td>
<td>IVDU</td>
<td>10</td>
<td>Lung abscess</td>
<td>BAL, sputum</td>
<td><em>S. typhimurium</em></td>
<td>Survived</td>
</tr>
</tbody>
</table>

*PR=present report; HS=homosexuality; NR=not reported; PLNA=percutaneous lung needle aspiration.

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**Table 2—Comparison Between Patients With and Without Salmonella Lung Disease During Salmonella Bacteremia**

<table>
<thead>
<tr>
<th>SLD</th>
<th>With (n=8)</th>
<th>Without (n=43)</th>
<th>p Value</th>
<th>NS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, yr</td>
<td>27</td>
<td>30</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Sex, male/female</td>
<td>8/0</td>
<td>35/8</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>IVDU (%)</td>
<td>7/8 (57)</td>
<td>33/43 (77)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Mean CD4 count/mm$^3$</td>
<td>73</td>
<td>70</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Prior lung disease (%)</td>
<td>3/8 (37)</td>
<td>18/43 (42)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>S. enteritidis (%)</td>
<td>6/8 (75)</td>
<td>24/43 (56)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>S. typhimurium (%)</td>
<td>2/8 (25)</td>
<td>15/43 (35)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Median survival, d</td>
<td>626</td>
<td>436</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

*SLD=Salmonella lung disease; NS=not significant.
infected patients as compared to other immunodepressed hosts.\textsuperscript{12,13} This low mortality possibly reflects the low pathogenicity of Salmonella in the respiratory tract.

There is no clear explanation as to why Salmonella produces pulmonary disease. All patients in our study had positive blood cultures, suggesting a hematogenous dissemination, but we selected this population. Aspiration of infected gastric secretions does not seem to be the source of infection, due to the low frequency of GI symptoms or isolation of Salmonella in stool cultures.\textsuperscript{7-10} The association of Salmonella with late HIV infection may reflect a predisposition for colonization of lungs previously damaged by HIV-related opportunistic infections. However, these patients had similar CD4+ cell counts than bacteremic patients without lung disease. Prior lung disease was not associated with a higher risk of lung involvement, in contrast to other immunocompromised patients. Because the Salmonella isolated were of different serotypes, no predominance of a particular and more virulent serotype explains the suppurative disease.

An important finding in this study was the high prevalence of pulmonary disease due to other pathogens. Previous reports of Salmonella bacteremia in AIDS patients have not described the incidence of lung disease in their patients, but they were not focused to this point.\textsuperscript{7-10} Profeta et al\textsuperscript{10} described six patients with Salmonella bacteremia, one of whom had bilateral pulmonary infiltrates diagnosed as \textit{P. carinii} pneumonia. Glaser et al\textsuperscript{15} described two cases of \textit{P. carinii} pneumonia and one of cryptococcal pneumonia among eight cases of Salmonella bacteremia. Kamantia et al\textsuperscript{20} studied \textsuperscript{222} HIV-infected patients admitted to the hospital because of respiratory symptoms and they found concomitant Salmonella bacteremia in \textsuperscript{20} (9%), but they did not describe any Salmonella lung infection. Due to the possibility of superinfection, it is important to determine whether pneumonia is due to Salmonella or to secondary infection by another organism,\textsuperscript{21} and it is not valid to assume that isolation of Salmonella from blood cultures in addition to a compatible clinical and radiologic picture mandate the diagnosis of nontyphoidal Salmonella pulmonary infection. Moreover, two patients in our study had coinfection with another pulmonary pathogen, a situation in which it is difficult to recognize the role of Salmonella in lung disease.

In summary, this retrospective analysis presents data from a 9-year-period in HIV-infected patients with Salmonella bacteremia and lung involvement at a tertiary hospital. To our knowledge, this report represents the first in which there has been a comprehensive study of pulmonary pathogens in AIDS patients with Salmonella bacteremia. Lung involvement due to nontyphoidal strains of Salmonella arises with severe immunodepression, with a subacute onset, without GI symptoms in most patients, and without specific predisposing factors. Lung abscess or cavitary pneumonia was the most frequent radiologic pattern. Due to the high incidence of superinfection in these immunodepressed patients, definite Salmonella pulmonary infection could be confirmed only by isolation of Salmonella species from respiratory samples. Our results emphasize the need for a definitive diagnosis of pulmonary infiltrates in HIV-positive patients with Salmonella bacteremia.

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