Outbreak of Legionnaires’ disease in immunosuppressed patients at a cancer centre: usefulness of universal urine antigen testing and early levofloxacin therapy

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ABSTRACT

This report describes an outbreak of Legionnaires’ disease in severely immunosuppressed patients hospitalised at a cancer centre. Universal urine antigen testing and early levofloxacin therapy appeared to lower case fatality rates in comparison with previous reports concerning this high-risk population. This diagnostic and therapeutic strategy should be considered when facing a nosocomial outbreak of Legionnaires’ disease in immunosuppressed hosts.

Keywords Immunosuppressed patients, Legionnaires’ disease, levofloxacin therapy, nosocomial outbreak, pneumonia, urine antigen testing

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A reduction in case fatality rates among non-immunosuppressed patients with Legionnaires’ disease (LD) has recently been observed, suggesting that new management strategies may result in improved outcome [1–6]. These new approaches include the use of urinary antigen testing for rapid diagnosis in combination with highly active antimicrobial agents against Legionella, e.g., azithromycin and fluoroquinolones [7,8]. However, little is known about the potential impact of these new strategies on immunosuppressed patients, who have the highest mortality rates. Accordingly, this report describes the impact of these new diagnosis and treatment strategies on an outbreak of LD caused by Legionella pneumophila serogroup 1 among severely immunosuppressed patients hospitalised at a cancer centre.

The outbreak of LD occurred over a 4-week period among patients in a 300-bed tertiary referral cancer centre for adults in Barcelona, Spain. The hospital opened in 1991 and no previous cases of nosocomial LD had been observed. The first case of Legionella pneumonia was detected on 24 February 2005. When two further cases were diagnosed within 48 h, Legionella urinary antigen testing was instituted for all patients hospitalised in the same wards as the first three cases, and for any patient presenting with a new onset of fever or respiratory symptoms (n = 155 patients). L. pneumophila serogroup 1 antigen in urine was detected using the NOW Legionella Urinary Antigen test (Binax, Scarborough, MA, USA). The test was performed on a 24-h basis, 7 days a week. To exclude false-positive results, all urine samples were boiled and concentrated. All patients with a positive urine antigen test underwent a chest radiograph and were given early intravenous levofloxacin therapy, whether or not they presented with pneumonia.

Samples for microbiological investigations were obtained from patients with pneumonia whenever possible, and also from the water system supply. All samples were cultured on selective buffered charcoal yeast extract-x medium, and pulsed-field gel electrophoresis typing was performed for all isolates [9].

The attributable case fatality rate was defined as death during symptomatic infection or as a consequence of its complications. The overall case fatality rate was defined as death from any cause within 28 days of the diagnosis. Table 1 shows the characteristics of the 12 patients involved in the outbreak. Three patients had profound neutropenia (<0.1 x 10⁹ cells/L), and one also had invasive pulmonary aspergillosis; this patient’s condition was complicated by diffuse alveolar haemorrhage, requiring mechanical ventilation.
Table 1. Baseline characteristics, clinical features and outcome of 12 immunosuppressed patients involved in a nosocomial outbreak of Legionnaires’ disease in a cancer centre

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (years)</th>
<th>Gender</th>
<th>Underlying disease</th>
<th>Immunosuppressive therapy</th>
<th>Clinical symptoms</th>
<th>Radiological findings</th>
<th>Treatment</th>
<th>Outcome/ time to death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>41</td>
<td>Male</td>
<td>Disseminated, cancer, central nervous system metastases, Lung cancer</td>
<td>Corticosteroids</td>
<td>Dyspnoea, diarrhea</td>
<td>Left lower lobe infiltrate</td>
<td>Clarithromycin (500 mg twice daily)</td>
<td>Died/≤24 h</td>
</tr>
<tr>
<td>2</td>
<td>81</td>
<td>Male</td>
<td>Lung cancer</td>
<td>Corticosteroids</td>
<td>Fever, respiratory symptoms</td>
<td>Right upper lobe infiltrate</td>
<td>Levofloxacin (500 mg daily)</td>
<td>Died/18 days</td>
</tr>
<tr>
<td>3</td>
<td>41</td>
<td>Male</td>
<td>Aplastic anaemia</td>
<td>Corticosteroids, cytotoxic chemotherapy, cyclosporine</td>
<td>Fever, respiratory symptoms</td>
<td>Bilateral infiltrates, cavitation</td>
<td>Levofloxacin (500 mg daily), Cyclosporine stopped</td>
<td>Survived</td>
</tr>
<tr>
<td>4</td>
<td>61</td>
<td>Male</td>
<td>Lung cancer</td>
<td>Corticosteroids, radiotherapy</td>
<td>Dyspnoea</td>
<td>Right lower lobe infiltrate</td>
<td>Levofloxacin (500 mg daily)</td>
<td>Survived</td>
</tr>
<tr>
<td>5</td>
<td>43</td>
<td>Female</td>
<td>Acute myeloid leukaemia, neutropenia, Lymphoma, neutropenia</td>
<td>Cytotoxic chemotherapy</td>
<td>Fever, respiratory symptoms</td>
<td>Multilobar infiltrates on the left lung</td>
<td>Levofloxacin (500 mg daily), Cyclosporine</td>
<td>Survived</td>
</tr>
<tr>
<td>6</td>
<td>74</td>
<td>Female</td>
<td>Lymphoma, neutropenia</td>
<td>Corticosteroids, cytotoxic chemotherapy</td>
<td>Malaise, diarrhoea</td>
<td>Left lower lobe infiltrate</td>
<td>Levofloxacin (500 mg daily), Cyclosporine</td>
<td>Survived</td>
</tr>
<tr>
<td>7</td>
<td>68</td>
<td>Male</td>
<td>Chronic lymphocytic leukaemia, haemolytic anaemia</td>
<td>Corticosteroids</td>
<td>Asymptomatic</td>
<td>Left lower lobe infiltrate</td>
<td>Levofloxacin (500 mg daily), Cyclosporine</td>
<td>Survived</td>
</tr>
<tr>
<td>8</td>
<td>57</td>
<td>Female</td>
<td>Acute lymphocytic leukaemia, neutropenia, invasive pulmonary aspergillosis</td>
<td>Corticosteroids, cytotoxic chemotherapy</td>
<td>Fever, respiratory symptoms, diffuse alveolar haemorrhage</td>
<td>Bilateral infiltrates</td>
<td>Levofloxacin (500 mg twice daily), Intensive care unit admission, mechanical ventilation, survived</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>68</td>
<td>Female</td>
<td>Lymphoma</td>
<td>Corticosteroids, cytotoxic chemotherapy</td>
<td>Fever</td>
<td>Right lower lobe infiltrate</td>
<td>Levofloxacin (500 mg daily)</td>
<td>Survived</td>
</tr>
<tr>
<td>10</td>
<td>54</td>
<td>Female</td>
<td>Lymphoma</td>
<td>Corticosteroids</td>
<td>Asymptomatic</td>
<td>No abnormal findings</td>
<td>Levofloxacin (500 mg daily)</td>
<td>Survived</td>
</tr>
<tr>
<td>11</td>
<td>71</td>
<td>Male</td>
<td>Pancreatic cancer</td>
<td>Corticosteroids</td>
<td>Asymptomatic</td>
<td>No abnormal findings</td>
<td>Levofloxacin (500 mg daily)</td>
<td>Died/21 days</td>
</tr>
<tr>
<td>12</td>
<td>57</td>
<td>Female</td>
<td>Lung cancer</td>
<td>Corticosteroids, cytotoxic chemotherapy</td>
<td>Fever, respiratory symptoms</td>
<td>Left lower lobe infiltrate</td>
<td>Levofloxacin (500 mg daily)</td>
<td>Survived</td>
</tr>
</tbody>
</table>

Ten of the 12 patients involved in the outbreak presented with pneumonia. The most frequent clinical symptoms in these ten patients were fever and respiratory symptoms, although two patients presented with atypical symptoms and one was asymptomatic, despite a chest radiograph demonstrating a new pulmonary infiltrate. Two additional patients were completely asymptomatic at the time when urine antigen testing was performed. Patient no. 3 presented with a large lung cavitation, persistent fever and persistent positive sputum cultures, but his condition steadily improved, with eventual full recovery.

The index patient (no. 1) was diagnosed initially with atypical pneumonia and was treated with clarithromycin. Despite early initiation of macrolide therapy, the patient’s clinical condition rapidly worsened, with death occurring within 24 h of the diagnosis of pneumonia. Once an outbreak of LD was suspected and universal urine antigen testing was performed, all patients were treated with levofloxacin, including the two patients with asymptomatic infection. Two more patients died within 28 days, but their deaths were considered to be unrelated to the infection. One patient (no. 2) had a rapid progression of underlying lung cancer with liver metastases, with death occurring on the 18th day of levofloxacin treatment, at which time all signs and symptoms of pneumonia had disappeared. The second patient with a positive urine antigen test without pneumonia (no. 11) was treated with levofloxacin as an outpatient, but died 21 days later during a subsequent period of hospitalisa-
tion because of local cancer progression and massive gastrointestinal bleeding. The attributable case fatality rate was 8.3% (one of 12 patients), and the overall case fatality rate (≤28 days) was 25% (three of 12 patients). 

*L. pneumophila* serogroup 1 was isolated from five sputum samples obtained from five patients with pneumonia, and also from several samples obtained from the water system supply. Pulsed-field gel electrophoresis typing indicated that all the isolates from water systems were identical and were clonally related to the isolates from sputum samples. The outbreak, which lasted 4 weeks, was successfully controlled by measures that included the immediate restriction of water use, and repeated superheating and flushing of the water system. After the outbreak, a copper–silver ionisation unit was installed to provide permanent reservoir disinfection in conjunction with ongoing active surveillance of the water system.

The baseline characteristics of the patients described here are similar to those found in earlier studies of LD in immunosuppressed hosts that reported overall case fatality rates of 50–80% [10,11]. A previous outbreak occurred during 1985 in a nearby hospital among immunosuppressed patients with cancer [10]. At that time, *Legionella* urine antigen testing was not available, and all patients were treated with erythromycin (plus rifampicin in some cases). The case fatality rates in the present study were substantially lower than those in the previous outbreak (attributable case fatality rates of 8% vs. 43%, and overall case fatality rates of 25% vs. 50%, respectively).

The present results are in line with recent reports involving non-immunosuppressed patients with community-acquired LD, indicating that early diagnosis, by means of urine antigen testing and fluoroquinolone therapy, may improve patient outcome [3–6]. In the outbreak reported here, universal urine antigen testing allowed asymptomatic patients to be identified at an early stage of *Legionella* infection. The prompt treatment of these patients may have modified the course of their infection and avoided the development of pneumonia and a more severe disease.

Fluoroquinolones have been shown to be more effective than older macrolides in inhibiting the intracellular growth of *L. pneumophila*, both in vitro and in animal models [12–14]. Improved outcome (with respect to time to defervescence and length of hospital stay) for patients treated with levofloxacin has been documented in three observational studies [4–6]. The results of the present study provide additional information regarding the usefulness of early monotherapy with levofloxacin for treatment of LD in severely immunosuppressed patients. However, while the low patient mortality was probably related to both universal urine antigen testing and prompt levofloxacin therapy, the small sample size and uncontrolled nature of the study mean that other testing and therapeutic strategies could have produced similar results. Nevertheless, the results suggest that the combined use of universal urine antigen testing and early treatment with levofloxacin might improve the outcome for severely immunosuppressed patients with LD. This diagnostic and therapeutic strategy merits consideration when facing a nosocomial outbreak of LD involving similar patient populations.

**ACKNOWLEDGEMENTS**

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**REFERENCES**

Detection of diverse SCCmec variants in methicillin-resistant Staphylococcus aureus and comparison of SCCmec typing methods


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ABSTRACT

Non-duplicate methicillin-resistant Staphylococcus aureus (MRSA) isolates (n = 436), collected from four hospitals located in three Korean cities between 2001 and 2005, were investigated by SCCmec typing and multilocus sequence typing (MLST). Variations within SCCmec, especially type II, were detected in 165 (37.8%) isolates, and these variants were characterised using four different SCCmec typing methods. The predominant SCCmec type was a type II variant that differed from type II by the absence of a pUB110 insertion. MLST analysis showed that most of the isolates carrying SCCmec variants belonged to ST5.

Keywords Methicillin-resistant Staphylococcus aureus, multilocus sequence typing, SCCmec variants, typing

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SCCmec is a mobile element, comprising the mec gene complex, the ccr gene complex and the junkyard (J) regions, which can integrate into the Staphylococcus aureus chromosome [1,2]. In 2001, Ito et al. [1] described three types of SCCmec elements (designated I–III), based on the structure of the mecA complex and the ccrAB allele. Subsequently, SCCmec type IV was identified, initially in two community-acquired strains of methicillin-resistant S. aureus (MRSA) [2,3]. In 2002, Oliveira and de Lencastre [4] developed a single-step multiplex PCR (M-PCR) method designed to provide maximum resolution of the various structural variants of the SCCmec element, based on genes located within the J-regions of SCCmec elements. Although this method did not include identification of the ccrAB allele, it enabled discrimination of the four major SCCmec types and certain variants, such as IA and IIIA. This method is simple and easy to perform, and has therefore been used increasing, but is limited by its inability to detect the newly identified SCCmec type V and subtypes IVa–IVd [5,6]. Subsequently, Zhang et al. [7] developed a new M-PCR strategy that has the advantage of identifying the J1 region of eight SCCmec elements (I, II, III, IVa–IVd and V) simultaneously.

In the present study, the SCCmec structural type and sequence type (ST) of 436 clinical isolates of MRSA were determined. The isolates were collected from four hospitals located in three Korean cities between 2001 and 2005. All isolates were tested for phenotypic resistance to oxacillin by the salt agar dilution method according to CLSI (formerly NCCLS) guidelines [8], and for the presence of the mecA gene by PCR.

To determine the SCCmec structural type, the M-PCR developed by Oliveira and de Lencastre...