ORIGINAL ARTICLE

Impact of positive legionella urinary antigen test on patient management and improvement of antibiotic use

J Garbino, J-E Bornand, I Uçkay, S Fonseca, H Sax

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See end of article for authors' affiliations

Correspondence to: Dr J Garbino, Division of Infectious Diseases, Department of Internal Medicine, University of Geneva Hospitals, 24, rue Micheli-du-Crest, 1211 Geneva 14, Switzerland; jorge.garbino@hcuge.ch

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Aim: To assess the incidence of legionella infection over a 27 month period at a large university hospital.
Material and Methods: The present retrospective cohort study enrolled patients with legionellosis, defined as those presenting a positive urinary antigen for legionella together with a medical history, clinical findings, and radiological findings consistent with pneumonia. These patients were evaluated to determine the relation between their test results and changes in treatment modalities. A control group of patients with pneumonia but a negative urinary antigen test for legionella were also analysed.
Results: Twenty seven of 792 assessed patients tested positive for legionella. In 22 of these patients, legionella active antibiotics were administered empirically. In seven patients, the test results prompted a legionella specific treatment, whereas in 12 cases, non-specific antibiotics were stopped within 24 hours. Overall, treatment was altered in more than half of the patients as a result of the test results.
Conclusions: The urinary antigen may have a direct impact on clinical management of pulmonary legionellosis. However, patient comorbidities and individual clinical judgment are still important for determining the best treatment to be given in each individual case.

Legionnaires' disease is an important cause of community and hospital acquired pneumonia.[1] It figures prominently among the four most common causes of community acquired pneumonia requiring hospitalisation.[2] Among these pneumonias, legionellosis is a severe disease with a mortality rate of up to 20%.[1] The aetiological diagnosis of legionellosis was difficult before the introduction of the urinary antigen test. The clinical symptoms of the disease are not specific for legionellosis and do not contribute to establishing an accurate diagnosis.[3] Laboratory evaluation requires expertise and involves specific culture media that are only used upon clinical suspicion of legionellosis.[4] Direct immunofluorescence tests are operator dependent and of low yield. Serological testing does not have an impact on patient management because seroconversion occurs relatively late in the course of infection.

> ''The aetiological diagnosis of legionellosis was difficult before the introduction of the urinary antigen test''

Legionella is susceptible to various classes of antibiotics, except for betalactams, cephalosporins, and carbapenems, both in vitro and in clinical disease.[1] Drugs of choice include macrolides—such as erythromycin, clarithromycin, or azithromycin—and fluoroquinolones—such as ciprofloxacin, levofloxacin, or moxifloxacin—with a recommended treatment duration of three weeks.[5]

The urinary antigen test facilitates the diagnosis of a large number of cases of *Legionella pneumophila* pneumonia, and is therefore extremely useful to clinicians for both diagnosis and therapeutic decision making. We investigated the impact of the urinary antigen test on patient management, with respect to therapeutic decision making on an everyday basis.

METHODS

Setting and laboratory procedures

The University of Geneva Hospitals, Switzerland, comprises a tertiary care institution featuring 1200 acute care and 1000 longterm care beds, with 45 000 annual admissions. The institution's virology laboratory receives all the hospital's samples for legionella urinary antigen testing.

A commercially available enzyme immunoassay kit (Legionella Urine Antigen EIA®; Biotest AG, Dreieich, Germany) was introduced into the clinical setting in 1997. This test is designed to detect *L pneumophila* serogroup 1 (sensitivity, 94.6%), but also has some crossreactivity with other serogroups (86% sensitivity for serogroups 2, 3, 4, 6, and 10), in addition to other legionella species.[6] The kit is a standard ''sandwich'' enzyme linked immunosorbent assay, which uses a polyclonal rabbit antiserum to capture soluble antigen and peroxidase labelled rabbit antibodies to detect immobilised antigen. Specificity is reported to be 100%, and sensitivity is reported to be 94.6% for *L pneumophila* serogroup 1 and 86% for legionellosis of any serogroup.[6] In another study, sensitivity was reported to be 76% for community acquired cases.[7]

Study design

This was a retrospective, descriptive, cohort study over a period of 27 months encompassing all adult patients with legionellosis admitted to our hospital and patients with nosocomial legionellosis. A patient with legionellosis was defined as presenting a positive urinary antigen test along with a medical history and clinical and radiological findings consistent with pneumonia (new infiltrates on chest *x* ray). In addition, at least two of the following findings were included: cough or increasing severity of cough, acute changes in the quality of sputum, fever, auscultatory findings such as rales or evidence of pulmonary consolidation, dyspnoea, and leucocytosis.[8] According to the Centers for Disease Control and Prevention, a nosocomial case required onset of pneumonia symptoms after 10 days of hospitalisation, and a probable nosocomial case exhibited onset between the second and 10th day of hospitalisation.[9] The remaining cases were considered to be community acquired. The urinary antigen result was assumed to have an impact on the initiation of legionella active treatment or the stopping of non-active treatment if active treatment was initiated or

Table 1 Characteristics of the 27 study patients with pneumonia and positive urinary antigen test

	Sex	Age (years)	Diagnosis at admission	Main underlying diseases	Stay in ICU/FO	Delay between A and T*	Delay between T and R*	Delay between R and ST†*	Delay between R and NST*	Nosocomial legionellosis	Impact‡
1	Female	60	Fulminant hepatitis	Diabetes	Yes/Yes	11	1	NA	NA	Definite	No/No
2	Male	50	Pneumonia	None	Yes/No	4	1	−5	0	No	No/Yes
3	Male	59	Pneumonia	Thrombosis	No/No	2	1	0	2	No	Yes/No
4	Female	30	Fever/ neutropenia	HD	No/No	2	0	0	10	No	Yes/No
5	Female	37	Pneumonia	AIDS, HCV	No/No	1	3	0	4	No	Yes/No
6	Female	46	Pneumonia	Alcoholism	No/No	3	1	−3	0	No	No/Yes
7	Male	60	Pneumonia	Stroke, hypertension	No/No	4	2	−5	0	No	No/Yes
8	Male	47	Pneumonia	None	Yes/No	2	0	−2	1	No	No/Yes
9	Female	3	Fallot's tetralogy	Fallot's tetralogy, PC	Yes/No	20	2	−2	2	Definite	No/No
10	Female	82	Myocardial infarct	Heart disease, WG	Yes/No	12	3	−3	−3	Definite	No/No
11	Female	78	Pneumonia	Hypertension	Yes/No	1	2	−2	0	No	No/Yes
12	Female	43	Pneumonia	None	No/No	0	2	0	0	No	Yes/Yes
13	Male	39	Pneumonia	Pneumothorax	Yes/No	1	5	−5	2	No	No/No
14	Male	75	Pneumonia	CD	Yes/Yes	37	2	0	12	Definite	Yes/No
15	Male	61	Pneumonia	Hypertension	Yes/No	1	2	−2	1	No	No/Yes
16	Female	67	Pneumonia	Rheumatoid polyarthritis	No/No	3	0	−1	0	No	No/Yes
17	Female	63	Pneumonia	COPD	Yes/No	0	4	−3	−4	No	No/No
18	Male	39	Pneumonia	AIDS	No/No	0	4	−4	0	No	No/Yes
19	Male	58	Renal Insufficiency	GS, renal transplantation	Yes/No	18	5	−7	5	No (infection during home leave)[10]	No/No
20	Male	78	Diverticulitis	Asthma	Yes/No	2	1	−1	−3	No	No/No
21	Male	74	Pneumonia	Cardiac failure	No/No	2	1	0	−2	No	Yes/No
22	Male	55	Pneumonia	Alcoholism	Yes/No	2	0	−2	3	No	No/No
23	Male	51	Pneumonia	Hypercholesterolaemia	No/No	2	2	−4	0	No	No/Yes
24	Female	75	Pneumonia	COPD	Yes/No	0	1	−1	13	No	No/No
25	Female	63	Pneumonia	Hypertension	No/No	1	2	0	0	No	Yes/Yes
26	Male	79	Pneumonia	Prostatic carcinoma	Yes/Yes	1	5	−6	2	No	No/No
27	Male	60	Pneumonia	Alcoholism	No/No	0	6	−3	0	No	No/Yes

*Measured in days; †negative values indicate that the patient had already been treated empirically with anti-legionella antibiotics; ‡impact of urinary antigen test on start of legionella treatment/stop of non-legionella treatment.
CD, cerebrovascular disease; COPD, chronic obstructive pulmonary disease; FO, fatal outcome; GS, Goodpasture's syndrome; NST, stopping of non-specific treatment; PC, pseudomembranous colitis; R, result; ST start of specific treatment; T, test; WG, Wegener's granulomatosis.

non-active treatment was stopped within one day of the availability of the test result, respectively.

The following study variables were extracted retrospectively from patient records using a standard protocol by an attending infectious diseases physician: patient's age and sex, date of symptom onset, date of hospitalisation, comorbidities, and date of initiation and termination of all antibiotic prescriptions during hospitalisation. Dates of urinary antigen test request and result reporting were extracted from the hospital's laboratory database.

For the same period, we also considered a group of patients as controls. They also had the diagnosis of pneumonia and a legionella urinary antigen test was performed. This control group consisted of 54 patients in whom the urinary antigen was negative, and we examined the impact of the test result on antibiotic treatment.

RESULTS

Patients

During the study period, 909 urinary antigen tests for *L pneumophila* were performed in 792 patients. The 27 (3.4%) patients who had positive results, 12 females and 15 males, formed the basis of our study. The median age was 60 years (range, 3–82). Eight patients were considered to be immunosuppressed (two AIDS, clinical category B2 and B3; two cancer, Hodgkin disease and colon carcinoma; two autoimmune diseases, Wegener's granulomatosis and Goodpasture's syndrome; one diabetes; one renal transplantation treated with cyclosporine), and six were smokers. All but three patients presented with at least one underlying disease (table 1). In 20 patients, pneumonia was recognised as the main diagnosis at the time of hospital admission. The remaining patients were admitted for myocardial infarction, fulminant hepatitis, fever and neutropenia, Fallot's tetralogy, renal insufficiency, and diverticulitis (table 1). There were four cases of nosocomial legionellosis and three cases were judged as travel associated. The remaining cases were deemed sporadic.

Laboratory results

Seven of nine patients had an additional positive culture result for *L pneumophila* serogroup 1. In six cases, direct fluorescent antibody testing was positive for respiratory secretions. The diagnosis was confirmed in only one patient by all three tests. In 15 patients, the urinary antigen test was the only positive laboratory test. In 13 patients, tracheal secretions were culture positive for legionella (11 bronchoalveolar lavage, two tracheal aspirations). In two patients, *Streptococcus pneumoniae* and *Escherichia faecalis* were isolated from bronchoalveolar lavage specimens as additional potential aetiological agents.

The median time from admission to legionella urinary antigen testing was two days (range, 0–37). In 18 patients, the test was ordered within 48 hours of admission, in 22 patients, within four days. Clinicians had to wait a median time of two days (range, 0–6) for the legionella urinary antigen result.

Treatment

All patients received empirical antibiotic treatment at admission, including a betalactam (16 patients), a cephalosporin

(six patients), a carbapenem (four patients), or a macrolide antibiotic alone (one patient). Initial treatment included legionella active antibiotics in 22 cases: 19 patients received clarithromycin, and three received erythromycin. Of the five remaining patients, four were given an appropriate treatment only upon receipt of the positive urinary antigen test result. One patient did not receive anti-legionella treatment at all because the diagnosis was determined after death.

In 12 patients, empirical treatment against pathogens other than legionella was stopped within 24 hours of establishing the aetiology of the disease. In four additional patients, this inappropriate treatment was stopped before the availability of the urinary antigen test result. In 10 patients, non-legionella treatment was continued despite the positive urinary antigen test. One patient died before the diagnosis was achieved.

In the control group (54 patients), 16 patients received initial antibiotic treatment with legionella active (two with fluoroquinolones, 14 with macrolides associated either with betalactams or cephalosporins). However, the duration of the combination treatment with macrolides was less than 10 days, as was treatment with the fluoroquinolones, because of the negative result of the urinary antigen test. Five patients did not receive antibiotic treatment. Thirty three patients received antibiotics that did not cover legionella and no antibiotics with legionella coverage were added.

Follow up

The median length of hospitalisation was 23 days (range, 5–74). Fifteen patients were hospitalised at the intensive care unit because they required ventilator support. Three patients in the intensive care unit died from legionella pneumonia—two had an antibiotic coverage for legionella and one did not. For this last patient, the positive urinary antigen was available only after death. No relapse occurred. In survivors, the median duration of treatment with legionella active antibiotics was 21 days (range, 15–32).

DISCUSSION

This retrospective evaluation showed that the legionella urinary antigen test had a major impact on everyday patient management. Most importantly, a positive urinary antigen test prompted the withdrawal of antibiotic treatment directed at non-legionella pathogens. This is a crucial issue, because restricting antibiotic treatment helps to reduce potential adverse effects, the development of antibiotic resistance, and treatment costs.

In the control group, 16 of the 54 patients received antibiotics with legionella coverage, but the treatment duration (< 10 days) was not adapted for the treatment of legionella pneumonia because of the negative urinary antigen result. For the other control group patients, no legionella specific antibiotic coverage was administered.

> ''Most importantly, a positive urinary antigen test prompted the withdrawal of antibiotic treatment directed at non-legionella pathogens''

In addition, the results of the legionella urinary antigen test prompted the initiation of an effective treatment against legionellosis, although this was of less importance because most of our patients with legionnaires' disease had already received antibiotics active against legionella empirically at the time the test result became available. This is in accordance with international guidelines advising that legionella specific antibiotics should be given to patients with community acquired pneumonia if some relevant clinical or epidemiological findings suggest this aetiology.[5] For nosocomial pneumonia, however, the first antibiotic choice does not necessarily include a legionella specific treatment.[5] In the four nosocomial cases documented in our study, such coverage was provided even though nosocomial legionellosis occurred infrequently at the study hospital.

Take home messages

- In over two thirds of cases, the urinary legionella antigen test had a direct impact on the clinical management of pulmonary legionellosis
- In seven patients, the test results prompted a legionella specific treatment, whereas in 12 cases, non-specific antibiotics were stopped within 24 hours
- Thus, the urinary antigen can have a direct impact on clinical management of pulmonary legionellosis, although patient comorbidities and individual clinical judgment are still important for determining the best treatment to be given in each individual case

In the control group, 16 of the 54 the patients received initial antibiotic treatment with legionella coverage, but the duration of the treatment with macrolides, alone or in combination, or with fluoroquinolones, was less than 10 days because of the negative result of the urinary antigen test. Treatment duration is another reason why establishing a definitive diagnosis is of importance. Legionnaires' disease requires a longer antibiotic course than most of the more common causes of community acquired pneumonia.[5] Failure to use a longer course could result in relapse.

As with any case series, our study findings are restricted to diagnosed cases. The low proportion of positive test results among all tests reveals the propensity of clinicians to rule out legionella as the cause of pneumonia. Furthermore, it is understood that urinary antigen tests have several shortcomings that are not evident in the results reported here. Such tests have reduced sensitivity in the first days after infection and in detecting non-*L pneumophila* serogroup 1 strains, and they lack the power to elucidate the strain related source of infection. For this reason, even though the results of our study support the use of the urinary antigen test, classic culture techniques for use in diagnosis are not to be neglected.

In conclusion, in over two thirds of cases, the urinary antigen had a direct impact on the clinical management of pulmonary legionellosis. However, other patient comorbidities and individual clinical judgment will continue to be important for determining optimal treatment for each individual case.

Authors' affiliations

J Garbino, I Uçkay, S Fonseca, H Sax, Division of Infectious Diseases, Department of Internal Medicine, University of Geneva Hospitals, 1211 Geneva 14, Switzerland
J-E Bornand, Clinical Virology Laboratory, Department of Internal Medicine, University of Geneva Hospitals

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