www.biogenericpublishers.com

Article Type: Case Report

Received: 12/05/2022

Published: 06/06/2022

Open Access Journal of Biogeneric Science and Research
ISSN 2692-1081

DOI: *10.46718/JBGSR.2022.11.000280*

A multidisciplinary approach to discern a false-positive result of the Legionella pneumophila urinary antigen test in an Italian teaching hospital: case report and epidemiological investigation

Alberto Tulipani[1], Beatrice Casini[2], Massimo Mentasti[3], Michele Totaro[2], Benedetta Tuvo[2], Andrea Porretta[2], Angelo Baggiani[2]*

[1]*Azienda Ospedaliero Universitaria Pisana, Pisa, Italy*
Via Paradisa 2, 56124 Pisa (Italy)
[2]*Department of Translational Research, N.T.M.S., University of Pisa, Pisa, Italy*
Via San Zeno 37, 56127 Pisa (Italy)
[3]*Microbiology Cardiff, Public Health Wales, University Hospital of Wales, Cardiff, UK*

*Corresponding author: Angelo Baggiani, Department of Translational Research, N.T.M.S., University of Pisa, Pisa, Italy

ABSTRACT

Legionnaires' disease (LD) diagnosis involves demonstration of infection by any of Legionella species and this is usually done by detection of specific antigens from urinary samples. However, the available Urine Antigen Test (UAT) recognizes only Legionella pneumophila serogroup 1 antigens and, besides being rapid and specific, still bears a considerable risk of misdiagnosis. This is a report of how a thorough epidemiological investigation, the good knowledge of the laboratory methods in use and the clinical reassessment of the patient all together led to the definition of a false positive UAT for LD. An 86yo man was admitted with respiratory distress to the Emergency Department (ED) of an Italian hospital. During ED admission no fever was observed, but proteinuria and urinary infection were subsequently detected. Patient was thus admitted to a Medical ward where, in consideration of the radiological findings and the respiratory distress, Legionella UAT was requested among other baseline laboratory exams. After the positivity of UAT the Infection Control Team (ICT) was involved to exclude a Legionella water contamination in hospital and patient's home networks. Afterwards, the ICT requested a repetition of the UAT on another sample, performing a preliminary urine sample centrifugation as described in Italian guidelines. This new UAT turned out negative and the ICT was thus convinced of the false positive condition of the first test.

This notable false positive result is yet another demonstration of why at least secondary level laboratories should yield the potential of another diagnostic tool for Legionnaires' disease, notably real-time PCR. The hospital Infection Control team, by means of an active collaboration with the microbiology laboratory and the clinical wards, is able to promote an evidence-based appropriate use of healthcare resources and an effective antimicrobial stewardship.

Keywords: Legionnaires' disease, Legionella pneumophila, Urine Antigen Test, case report, antimicrobial stewardship, appropriateness.

Abbreviations: ABG: Arterial Blood Gas; CFU: Colony Forming Unit; ED: Emergency Department; ICT : Infection Control Team; LD: Legionnaires' disease; MIC: Minimal Inhibitory Concentration; NPV: Negative Predictive Value; PPV: Positive Predictive Value; PTCA: Percutaneous Transluminal Coronary Angioplasty; qPCR: quantitative Polimerase Chain Reaction; UAT: Urine Antigen Test.

Introduction

Legionnaires' disease (LD) is a severe form of pneumonia transmitted by inhalation of aerosolized water containing bacteria belonging to the Legionella genus, usually Legionella pneumophila, or, less commonly, by aspiration of contaminated drinking water [1-2]. Inter-human transmission of LD has never been demonstrated; only a single episode of possible person-to-person transmission of LD has been reported [3]. The gold standard for LD diagnosis is the isolation of Legionella species by culture from lower respiratory secretions, however as this procedure is quite time-consuming and requires dedicated media, the main mean of LD diagnosis is by detection of specific antigen from urine samples [1-4].

Urine Antigen Test (UAT) for LD employs specific monoclonal antibodies to recognize Legionella pneumophila serogroup 1 lipopolysaccharide antigens [1]. UAT is worldwide available and unlike cultural diagnostic methods it allows to diagnose LD rapidly. Currently almost all diagnoses of LD are obtained by UAT (97% both in the USA [1] and in Europe [5], including Italy [6]). However, for its ease of use, UAT is more frequently executed to exclude, rather than confirm, a diagnosis of atypical pneumonia which might be missed by conventional culture and/or serological methods [7-8]. Nevertheless, UAT is unable to detect LD caused by non-serogroup 1 strains of Legionella pneumophila or other Legionella species. For this reason a number of LD cases remain undiagnosed (20-50%) if only UAT is used as a diagnostic test [1, 9].

In Italy, despite both evidence from medical literature and the national guidelines for Legionella control suggest performing various tests (UAT, cultural methods, qPCR, immunofluorescence, ELISA test) to obtain a clear diagnosis, many hospital microbiology laboratories only offer the UAT as a diagnostic tool [7, 10-11]. Molecular diagnosis of LD by real-time PCR, in particular, is widely advocated [12-14].

Aim of this work is to underline limitations of the UAT as sole diagnostic approach for LD. The description of a notable case of false-positive UAT clarifies the importance of considering the pre-test probability when interpreting results. Appropriateness demands that all diagnostic tools are used with a clear and plausible hypothesis in mind and the good readiness of a test should never be an excuse to request it with lightness. An LD misdiagnosis bears potentially harmful consequences both in term of unnecessary drug therapy for the patient and inappropriate activation of corrective and preventive actions by the healthcare system.

Case presentation

Patient history and clinical tests

During the night between the 6th and the 7th of July 2017, an 86yo man was admitted with respiratory distress to the Emergency Department (ED) of Pisa University Hospital. Other than age, his risk factors were type 2 diabetes and advanced stage rectum adenocarcinoma. The malignancy had been diagnosticated in 2016 and surgically treated in February 2017; metastases were identified in 2018 and last cycle of chemotherapy was in April 2017. Clear disease progression was evident in June 2017 (secondary pulmonary lesions with pleural effusion, ascites, peritoneal carcinomatosis in increase with abdominal muscular wall infiltration). It is noteworthy that two therapeutic paracentesis (June and July 2017) became necessary to improve the respiratory compromise secondary to ascites. Patient's medical history also included chronic ischaemic heart disease (PTCA approximately 10 years before) and permanent atrial fibrillation.

During ED admission no fever was reported or observed. At physical examination normal breath sound was audible without abnormalities, except for the lung bases; the most notable finding was a tense abdomen for ascites with carcinomatosis. The arterial blood gas (ABG) test was consistent with metabolic acidosis, while the chest radiography (albeit only executed in antero-posterior supine projection) showed a faint pulmonary basal lesion on the right, bi-basal parenchymal dysventilation and bilateral pleural effusion.

The patient was thus admitted to a Medical ward where, in consideration of the radiological findings and the respiratory distress, Legionella UAT (Legionella Card LN-9020; Beta Diagnostici, Messina, Italy) was requested among other baseline laboratory exams. On the 7th of July afternoon the positivity of the Legionella UAT triggered the mandatory infectious disease notification procedure.

Epidemiological investigation and environmental samplings

As a recent hospitalization in the Geriatric ward at the end of June (27-29/06/17) was reported, the Infection Control team was involved to exclude a Legionella water contamination. The on-site visit at the Geriatric ward allowed to inspect the whereabouts of the patient during the previous hospitalization and to gain access to the medical record. An unscheduled water sampling for Legionella was performed in the Geriatric ward on the 10th of July as suggested by Italian guidelines [10]. Hot water samples were collected from the tap of the bathroom in the room where the patient had been hospitalized (point-of-use

Citation: Alberto Tulipani[1], Beatrice Casini[2], Massimo Mentasti[3], Michele Totaro[2], Benedetta Tuvo[2], Andrea Porretta[2], Angelo Baggiani[2*].A multidisciplinary approach to discern a false-positive result of the Legionella pneumophila urinary antigen test in an Italian teaching hospital: case report and epidemiological investigation. Op Acc J Bio Sci & Res 11(5),2022

DOI: *10.46718/JBGSR.2022.11.000280*

water filter present and within expiration date), from the tap of the common bathroom at the distal point of the ward (point-of-use water filter present and within expiration date) and from the tap (without filter) of the nurse station. Furthermore, hot water samples were collected in other wards of the same building.

Several confounding factors emerged and the Infection Control team requested a repetition of the Legionella UAT on another sample. An agreement was reached with the Microbiology Laboratory to perform a preliminary centrifugation of the urine sample as per Italian guidelines (12.000 g for 2 minutes) [10].

An independent water sampling was afterwards performed by the Local Health Authority. Samples were collected, before and after flaming, from the tap of the patient room, from the unfiltered tap in the nurse station and from the tank of the central water system. Further water samples were also collected from the patient's home.

Clinical results and therapy

The patient had never developed fever, neither at home, nor during the hospital stay. The patient had a long-term prescription, at least from June, of a small dose of methylprednisolone (16 mg od) which could have masked fever, even if unlikely considering the low dosage. Laboratory findings on blood tests were aspecific and consistent with the cancer staging (Table 1). Urinalysis was pathological for pH 5.0, albumin 30 mg/dl, hemoglobin 0.5 mg/dl, turbidity, Red Blood Cells 167/µL, White Blood Cells 4.098/µL and presence of bacteria. Urine culture results were not available at the time and later showed growth of Candida albicans (>1x105 CFU/mL).

The radiological findings (Figure 1) were not indicative of LD and the pulmonary lesion could have been consistent with the already known thoracic metastasis (a CT scan of June 2017 highlighted the appearance of two pulmonary secondary lesions, one of 6 mm in lingular paracardiac position, and the progression of the infero-external right mammary thoracic wall nodularity).

Levofloxacin was prescribed upon ward admission. To be noted that the respiratory distress got better after yet another paracentesis (the patient had two recent hospitalization for respiratory distress, in both cases effectively treated by paracentesis).

Results of the epidemiological investigation and environmental samplings

In the Geriatric ward, the point-of-use water filters were found within expiration date. The hot water network was

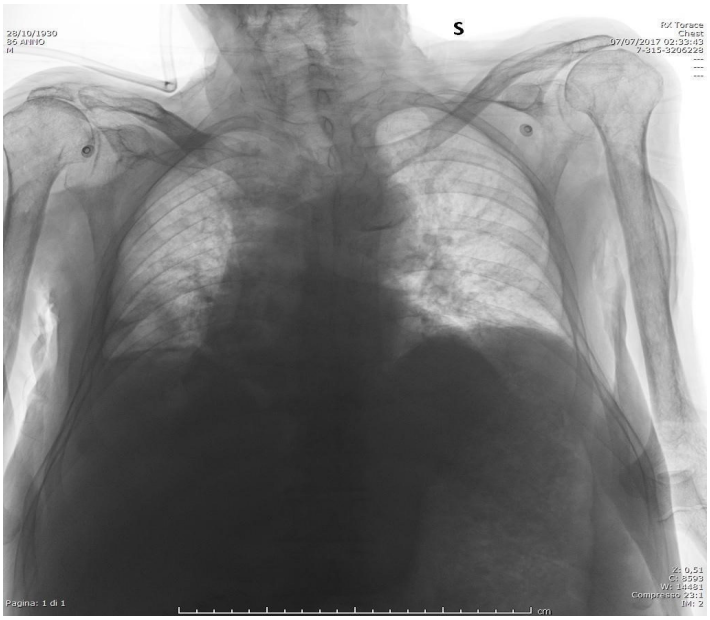

Figure 1: *Chest radiography (reverse contrast for image clarity).*

Table 1: *Summary of clinical results performed on patient's blood sample.*

Signaled Analysis	Possible interpretation
Total White Cells 18.190/uL Neutrophils 16.600/uL	Aspecific neutrophilic leukocytosis
Hemoglobin 12.1 g/dl, Mean Corpuscular Volume 83.4 fL Mean Corpuscular Hemoglobin 26.8 pg Mean Corpuscular Hemoglobin Concentration 32.1 g/dl	Mild normochromic normocytic anaemia consistent with a chronic disease
Coagulation panel and platelets (274.000/uL) within normality range	No signs of severe acute disease
C-Reactive Protein 5.29 mg/dl Erythrocyte Sedimentation Rate 58 mm/h	Aspecific mild elevation of inflammatory markers
Fasting glycemia 9.55 mmol/L Haemoglobin A1c protein 76 mmol/mol	Poorly controlled diabetes
Serum sodium levels 141 mEq/L	No signs of hyponatremia
Mild hypoalbuminemia calculated from serum protein electrophoresis 3.0464 g/dl (44.8% of 6.8 g/dl) Relative increase of alpha-1 (7.8%), alpha-2 (13.2%), beta 2 (8.4%) and gamma globulins (20.0%)	Mild aspecific inflammation

Citation: Alberto Tulipani[1], Beatrice Casini[2], Massimo Mentasti[3], Michele Totaro[2], Benedetta Tuvo[2], Andrea Porretta[2], Angelo Baggiani[2*].A multidisciplinary approach to discern a false-positive result of the Legionella pneumophila urinary antigen test in an Italian teaching hospital: case report and epidemiological investigation. Op Acc J Bio Sci & Res 11(5),2022

DOI: *10.46718/JBGSR.2022.11.000280*

appropriately chlorinated (> 0.3 mg/L of chlorine dioxide at the point-of-use) as suggested by the Italian Guidelines for Legionella control [10]. Hot water temperatures were found between 38 and 39°C, thus well below the value suggested by the Italian Guidelines (50°C) [10]. The patient's hospitalization had been brief (3 days within hospital, 2-2.5 within the Geriatric ward excluding the time spent in the ED). The patient was reported as extremely impaired in deambulation and in need of assistance for activities of daily living and instrumental activities of daily living. Therefore the patient's overall condition accounts for the shower lack of use during the hospital stay. Tap water was not used for aerosol therapy nor as drinking water.

The clinical record of the previous hospital stay in the Geriatric ward was reviewed for relevant information to be included in the epidemiological investigation. The patient had been admitted to hospital for respiratory distress (no fever reported) with a chest radiography (anteroposterior supine projection) negative for pulmonary lesions but with signs of bilateral basal dysventilation and costophrenic angles blunting. The symptoms improved after a therapeutic paracentesis and the patient was swiftly discharged. Considering the invasive procedure an antibiotic therapy had been prescribed (ciprofloxacin 500 mg bid for 4 days) and the medication had been realistically carried on at home. At discharge, a urine culture was in progress and two days later it was reported positive for Hafnia alvei (>1x105 CFU/mL), with a MIC for ciprofloxacin ≤0.25 µg/ml; so the prescribed antibiotic was judged appropriate and no further action was taken. Thus the Infection Control team was able to conclude that the respiratory symptoms were not exactly of new onset, but likely a recrudescence in the context of a known cancer-related complication. Furthermore, during the supposed incubation period for legionellosis, the patient had been taking an antibiotic active on Legionella. Finally, the recent bacteriuria was noted as a possible confounding factor for subsequent urinary samples.

On the 11th of July the repeated urinary Legionella antigen test turned out negative. The Infection Control team was thus convinced of the false positive condition of the first test. Water samples collected in the Geriatric Ward and in further wards of the same building did not show presence of Legionella. The Local Health Authority analysis revealed the presence of Legionella pneumophila serogroup 1 (100-400 CFU/L) in the unfiltered tap of the nurse station and in the tank of the central water system. Legionella was not found after tap sterilization and water flowing, proving a faucet colonization, not extended to the whole water network. The patient had no contact with the nurse station, however an unscheduled hyperchlorination was performed as preventive measure. The point-of-use water filtration and the water chlorination appeared effective as no other suspect case emerged during the same period. Finally, no Legionella was isolated from the patient's home.

Discussion and Conclusion

The Italian guidelines [10], in accordance with international scientific literature [1], report a 99-100% specificity for the Legionella urinary antigen test. However, the same guidelines warn against altered urinary samples, as in case of proteinuria or urinary infections [15]. They also state serum sickness [16] and Nocardia asteroides infections [17] as known causes of false-positivity.

1) Proteinuria

Serum sickness or the presence in urine of a rheumatoid-like factor were identified as confounding factors as pretreatment with a proteinase K demonstrated that the molecule causing false-positive results was a polypeptide [16]. Heating urine samples was also proposed as a pre-treatment to remove interfering antibodies or rheumatoid-like factors without affecting heat-stable urinary Legionella antigens [18]. In this case we did not have a clear diagnosis of proteinuria. However, it must be reminded that the patient had poorly controlled diabetes, likely not recently diagnosed, which can reasonably have caused a diabetic nephropathy with proteinuria. The urinalysis is no gold standard for proteinuria and the albuminuria value on spot urine analysis must be taken with caution when many cells, especially white blood cells, are detected. Finally, the hypoalbuminemia can indeed be a sign of a protein-losing nephropathy, but it is also a consequence of the malnutrition associated with the chronic inflammation linked to the cancer advanced stage.

2) Interfering microorganisms

Interfering microorganisms are also known to influence the results of the UAT in terms of false-positivity [15, 17]. The patient had a recent urinary positivity for Hafnia alvei, a gram-negative bacterium, and, at the moment of testing, Candida albicans was present in the urine.

3) Low pre-test probability

Finally, the implications of the Bayes theorem [19] must be taken under consideration. The patient medical history and examination did not suggest that LD was more likely than other diagnoses. All the symptomatology and the clinical findings could have been easily explained by the underlying oncological disorder. As a consequence, according to the Bayes theorem, when the pre-test probability is low, the negative predictive value is optimal while the positive predictive value is scarce [19].

To reduce the chance of false positive UAT results, the Italian guidelines [10] recommend boiling a 0.5-1 mL urine aliquot for 5 minutes and after centrifuging it at 12000 g for 2 minutes using the supernatant for the test. The Italian guidelines recommendation was not implemented in the routine activity, mainly because the official documentation of the UAT in use instructed to directly test the urinary sample. This discrepancy between the national guidelines and the user instructions of a diagnostic instrument is a critical point, especially as both have been approved by the same Ministry of Health.

This case report is valuable because it reveals the importance of considering the predictive value of a screening test such as the Legionella UAT. In case of doubt, a confirming second-step test is highly advisable and should be readily available. Culture analysis remains the reference standard for LD diagnosis [1, 20]. In a recent study sensitivity of UAT compared to culture was found to be 87%, specificity 94.7%, positive predictive value (PPV) 63.8% and negative predictive value (NPV) 98.5% [7]. However, culture analysis requires days and expertise and its sensitivity is only around 81% [1, 20].

Polymerase chain reaction (PCR) is rapidly emerging as a valid LD diagnostic technique [20-21]. Sensitivity of UAT compared to PCR was found to be 74.7%, specificity 98.3%, PPV 77.7%, and NPV 98.1% [7]. In a specific context, the implementation of PCR in clinical practice lowered the UAT specificity from 97.7% to 94.7% [7], thus exposing a number of false positive results. The combination of UAT and PCR enhances sensitivity without affecting specificity, therefore increasing the PPV [21]. During a recent LD outbreak, this rise in sensitivity (from 85.2% to 92.6%) and minor decrease in specificity (from 99.4% to 98.3%) was confirmed on the field [13]. In an Italian retrospective analysis, the addition of qPCR demonstrated a significant increase of sensitivity over the use of culture and/or UAT for diagnosis [14].

In conclusion, all LD test methods possess advantages and disadvantages, therefore clinicians should be able to use more than one in order to make a correct diagnosis. Relying only on one method, in particular UAT, bears an uncontrollable risk of false results [22]. A misdiagnosis is particularly dangerous as it carries the risk of administering drugs with possible adverse effects to persons that are not infected and would not have needed treatment. Fluoroquinolone antibiotics are under several black box warnings from the United States Food and Drug Administration, dating back from 2008 [23]. When prescribing antibiotics it is also necessary to consider the relevant effects not only on the single patient well-being, but also on the global health in terms of emerging multidrug resistant organisms. By helping to rule out false positive results, the Infection Control team, as suggested by the Italian Guidelines [10], is able to take an active role in an effective antimicrobial stewardship initiative.

Declarations

Ethics approval and consent to participate

No experimental work with humans or animals is included in this paper. Ethical Committee approval for human or animal research is therefore not necessary. On admission to hospital, the patient has signed a consent to authorise the use of his data in anonymous form for Public Health or Research purposes as stated in the "Patient privacy information sheet" of the Azienda Ospedaliero-Universitaria Pisana, in compliance with the Italian Privacy Act of 2003 (Decreto Legislativo 196/2003). Therefore, patient gave written consent for their personal or clinical details for this publication.

Availability of data and materials

Data are available to all interested researchers upon request to Azienda Ospedaliero Universitaria Pisana, in compliance with the Italian Privacy Act of 2003 (Decreto Legislativo 196/2003)

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author's contributors

Conceptualisation, A.B., B.C. and A.T.; Methodology, A.B., B.C. and A.P.; Investigation, A.T., M.T., A.P. and B.C.; Writing – Original Draft Preparation, A.T.; Writing – Review and Editing, M.T., B.C. B.T. and M.M.; Supervision, B.C., A.B.

Competing interests

The authors declare that there are no conflicts of interest.

Acknowledgements

We thank the hospital Staff for the data availability

References:

1. Pierre DM, Baron J, Yu VL, Stout JE (2017) Diagnostic testing for Legionnaires' disease. Ann Clin Microbiol Antimicrob 16:59.
2. Phin N, Parry-Ford F, Harrison T, Stagg HR, Zhang N, et al. (2014) Epidemiology and clinical management of Legionnaires' disease. Lancet Infect Dis. 14(10):1011-21.
3. Correia AM, Ferreira JS, Borges V, Nunes A, Gomes B, et al. (2016) Probable Person-to-Person Transmission of Legionnaires' Disease. N Engl J Med 374(5): 497-498.
4. European Centre for Disease Prevention and Control (ECDC) (2018)

European Union (EU) case definitions. Stockholm: ECDC; 2018.
5. European Centre for Disease Prevention and Control (ECDC) 2020. Annual Epidemiological report for 2018. Legionnaires' disease. Stockholm: ECDC; 2020
6. Italian National Institute of Health (2019) Rapporto annuale sulla Legionellosi in Italia nel 2018 [Annual Report of Italian Legionnaires' disease cases in 2018]; Italian National Institute of Health: Rome, Italy, 32: 1–24.
7. Peci A, Winter AL, Gubbay JB (2016) Evaluation and Comparison of Multiple Test Methods, Including Real-time PCR, for Legionella Detection in Clinical Specimens. Front Public Health.
8. Dionne M, Hatchette T, Forward K (2003) Clinical Utility of a Legionella pneumophila Urinary Antigen Test in a Large University Teaching Hospital. Canadian J. Infect. Dis 14: 85–88.
9. Vaccaro L, Izquierdo F, Magnet A, Hurtado C, Salinas MB, et al. (2016) First Case of Legionnaire's Disease Caused by Legionella anisa in Spain and the Limitations on the Diagnosis of Legionella non-pneumophila Infections. PLoS One. 11(7): e0159726.
10. Italian National Institute of Health (2018) Linee Guida per La Prevenzione Ed Il Controllo Della Legionellosi [Guidelines for prevention and control of legionellosis]. Rome, Italy: Italian National Institute of Health; 2015.
11. Svarrer CW, Luck C, Elverdal PL, Uldum SA (2012) Immunochromatic kits Xpect Legionella and BinaxNOW Legionella for detection of Legionella pneumophila urinary antigen have low sensitivities for the diagnosis of Legionnaires' disease. J Med Microbiol 61: 213–217.
12. Mentasti M, Kese D, Echahidi F, Uldum SA, Afshar B, et al. (2015) Design and validation of a qPCR assay for accurate detection and initial serogrouping of Legionella pneumophila in clinical specimens by the ESCMID Study Group for Legionella Infections (ESGLI). Eur J Clin Microbiol Infect Dis. 34(7): 1387-1393.
13. Gadsby NJ, Helgason KO, Dickson EM, Mills JM, Lindsay DS, et al. (2016) ESCMID Study Group for Molecular Diagnostics; ESCMID Study Group for Legionella Infections, Basel, Switzerland. Molecular diagnosis of Legionella infections--Clinical utility of front-line screening as part of a pneumonia diagnostic algorithm. J Infect 72(2): 161-170.
14. Ricci ML, Grottola A, Fregni Serpini G, Bella A, Rota MC, et al. (2018) Improvement of Legionnaires' disease diagnosis using real-time PCR assay: a retrospective analysis, Italy, 2010 to 2015. Euro Surveill. 23(50):1800032.
15. Helbig JH, Uldum SA, Lück PC, Harrison TG (2001) Detection of Legionella pneumophila antigen in urine samples by the BinaxNOW immunochromatographic assay and comparison with both Binax Legionella Urinary Enzyme Immunoassay (EIA) and Biotest Legionella Urin Antigen EIA. J Med Microbiol.50(6):509-516.
16. Deforges L, Legrand P, Tankovic J, Brun-Buisson C, Lang P, (1999) Case of False-Positive Results of the Urinary Antigen Test for Legionella pneumophila. Clin Infect Dis 29: 953–954.
17. Pontoizeau C, Dangers L, Jarlier V, Luyt CE, Guiller E, et al. (2014) Ruling out false-positive urinary Legionella pneumophila serogroup 1 and Streptococcus pneumoniae antigen test results by heating urine. J Clin Microbiol. 52(12): 4347-4349.
18. Bailleul E (2004) False-positive result with BinaxNOW Legionella Antigen immunochromatographic (ICT) assay: response to Helbig et al. (2001). J. Med. Microbiol 53: 173–173.
19. Medow MA, Lucey CR (2011) A qualitative approach to Bayes' theorem. Evid Based Med 16: 163–167.
20. Cristovam E, Almeida D, Caldeira D, Ferreira JJ, Marques T (2017) Accuracy of diagnostic tests for Legionnaires' disease: a systematic review. J. Med. Microbiol 66: 485–489.
21. Avni T, Bieber A, Green H, Steinmetz T, Leibovici L, et al. (2016) Diagnostic Accuracy of PCR Alone and Compared to Urinary Antigen Testing for Detection of Legionella spp.: a Systematic Review. J Clin Microbiol 54: 401–11.
22. Rota MC, Fontana S, Montaño-Remacha C, Scaturro M, Caporali MG, et al. (2014) Legionnaires' disease pseudoepidemic due to falsely positive urine antigen test results. J Clin Microbiol. 52(6):2279-80.
23. Tanne JH (2008) FDA adds "black box" warning label to fluoroquinolone antibiotics. BMJ 337: a816–a816.