Urine Antigen Tests Positive for Pontiac Fever: Implications for Diagnosis and Pathogenesis

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(See the article by Burnsed et al. on pages 222–8)

Pontiac fever takes its name from the Michigan city where an epidemic of a relatively mild febrile illness occurred in July 1968 [1]. Employees and visitors to the Pontiac Health Department became ill over a several-day period, with at least 144 people affected. The attack rate was very high in building occupants and visitors, with 95% of employees and 29% of visitors becoming ill. The illness manifested mainly as fever, headache, myalgia, and fatigue that lasted 2–5 days. Although a small fraction of persons with disease required months to recover from assorted neuropsychiatric symptoms, most recovered promptly without sequelae. Pneumonia was not documented in any person with disease. Epidemiologic investigation showed that the sole risk factor for the disease was being in the building, with an increased risk for disease in those who were in the building longer. The incubation period ranged from 5 to 66 h after building entry, with a median value of ∼36 h. Reentering the building after recovery from illness resulted in a lower attack rate (10%–45%), and ill patients had milder symptoms than during their first illness. Investigations for viral infections and for allergic reactions to known environmental allergens and toxins were unrevealing. A leak in the building’s air duct that allowed water from the evaporative condensing system to enter the circulating air was found to have resulted in the epidemic. Temporary cessation of air conditioning removed the risk of disease, whereas turning the system back on caused disease.

The implicated water condensate contained many different types of environmental microorganisms, including several different Pseudomonas, Corynebacterium, Bacillus, and Flavobacterium species. Guinea pigs placed in the affected building during the outbreak developed pulmonary nodules [2]. Furthermore, challenge of guinea pigs with aerosolized water from the evaporative condenser caused pneumonia in the animals, but they did not develop pneumonia when the water was filtered or autoclaved. Extensive microbiologic studies of the guinea pigs’ lungs failed to demonstrate a convincing etiologic agent, including aerosol challenge of guinea pigs with some of the microorganisms found in the implicated water.

Nine years after the Pontiac epidemic—and soon after the discovery of the etiology of legionnaires disease—Legionella pneumophila serogroup 1 was cultured from 40%–60% of the frozen lungs of the building-exposed and aerosol-challenged guinea pigs [2]. Serum specimens from 37 patients with Pontiac fever who had the most characteristic illnesses were tested for antibody to the guinea pig isolate [2]. Eighty-four percent of these patients had elevated antibody levels to the bacterium, whereas a control group of 10 unexposed people had no such antibodies detected.

Availability of an antibody test—and, later, the ability to isolate environmental Legionella bacteria—allowed the discovery of other outbreaks of Pontiac fever. Retrospective analysis of a Pontiac fever outbreak among workers who used pressure washers to clean industrial turbines led to the adoption of the term “legionellosis,” which is now used to describe Pontiac fever, legionnaires disease, and nonpneumonic infections caused by Legionella bacteria [3]. Several outbreaks of simultaneous Pontiac fever and legionnaires disease were described, although why some persons with disease develop legionnaires disease and others develop Pontiac fever has not been determined [3, 4]. Most aerosolized sources of bacterial-contaminated warm water, including whirlpool spas, warm spring pools, decorative fountains, cooling towers, and industrial cleaning systems that use high-pressure water, have been linked to outbreaks of Pontiac fever. Legionella species other than L. pneumophila have been cultured from epidemiologically implicated sites, and variable proportions (30%–85%) of affected people have had antibodies to...
the Legionella species detected in the environmental source [3, 5].

There is no agreed-upon definition of Pontiac fever. The diagnosis is usually made on the basis of epidemiologic, clinical, clinical laboratory, and environmental microbiology findings. Epidemiologic and clinical findings usually include a common-source outbreak of a short incubation period and a short-duration, nonfatal, nonpneumonic illness characterized by malaise, myalgia, and fever. Also usually required are proven exposure to an aerosolized environmental source containing Legionella bacteria and development of antibodies to the isolated bacterium in a significant fraction of affected people. Because several outbreaks have been investigated after biocides were added to an implicated source, only molecular evidence of the bacterium has been used in some case definitions. Neither the sensitivity nor the specificity of these findings is known, nor is it known specifically how to diagnose sporadic cases of the disease. Because Legionella species are ubiquitous in the environment, and because Legionella antibodies can be nonspecific, laboratory evidence of Pontiac fever can be nonspecific in sporadic cases [6]. Complicating this further is the possibility that, in some outbreaks, patients could have very mild legionnaires disease, with clinical findings intermediate between legionnaires disease and Pontiac fever. Recently, a proposed standard Pontiac fever definition was published elsewhere [7].

Whether Pontiac fever is due to Legionella infection is unknown. The very short incubation period is too brief to allow high-grade bacterial multiplication in the lung or elsewhere in the body. The absence of pneumonia, short duration of illness, recurrent milder illness with rechallenge, and complete recovery without antibiotic treatment also make Legionella infection very unlikely. In contrast to Pontiac fever, the incubation period for legionnaires disease is 2–18 days, with median values of 4–6 days. Patients with legionnaires disease who are not treated with specific antibiotics have a 20%–80% chance of death and have prolonged illnesses if they recover without receipt of specific antibiotic therapy.

The differences between the typical findings of legionnaires disease and those of Pontiac fever led the investigators of the 1968 Pontiac fever outbreak to speculate that the disease could be due to bacterial toxin inhalation or an allergic reaction to inhaled live or dead bacteria, with the inciting bacteria being either Legionella species or coexisting flora [1, 2]. Another speculation is that the inciting organism is a free-living amoeba commonly present in environmental sites containing Legionella bacteria [8]. It is known that the presence of Legionella antibodies can be nonspecific as a result of cross-reactions with a variety of bacteria, especially Pseudomonas aeruginosa. Whether inhalation of dead L. pneumophila can cause antibody formation in humans is unknown, but it is known that aerosol inhalation of L. pneumophila-purified membranes results in the production of bacterial antibodies in guinea pigs [9]. It is possible that the inhalation of non-Legionella bacterial endotoxin provides an adjuvant effect to inhaled (but low-dose) live or dead Legionella bacteria, resulting in an antibody response to Legionella bacteria and enhanced illness. One child with Pontiac fever had a tracheal culture positive for L. pneumophila, providing some support for the role of inhalation of live L. pneumophila in the pathogenesis of Pontiac fever [10]. Pontiac fever shares many similarities to illness caused by bacterial endotoxin inhalation, and 2 of 3 recent Pontiac fever investigations that looked for airborne endotoxin have shown elevated endotoxin levels at outbreak sites [11–14]. L. pneumophila makes a poorly pyrogenic endotoxin that is unable to bind to CD14, a major cellular endotoxin receptor, making this endotoxin an unlikely disease culprit [15]. Pontiac fever is probably due to exposure to a toxic mix of live and dead microorganisms and their products, including endotoxin made by non-Legionella bacteria, as well as low-dose live or dead Legionella bacteria incapable of causing pneumonia in the affected host. Reduced bacterial virulence seems to be an unlikely explanation, because there is no evidence that the L. pneumophila bacterium isolated from the 1968 Pontiac fever outbreak has reduced ability to grow in macrophages or reduced virulence in guinea pigs. However, in a Pontiac fever outbreak associated with exposure to Legionella anisa, there was evidence that the bacterium was avirulent in human cells and in guinea pigs [16]. Until the pathogenesis of Pontiac fever is better understood, it is more accurate to say that the disease is associated with exposure to Legionella species, rather than that it is caused by the bacterium.

In this issue of Clinical Infectious Diseases, Burnsed et al. [17] report a combined outbreak of Pontiac fever and legionnaires disease at a hotel in Oklahoma City, Oklahoma, associated with exposure to a poorly maintained hot tub. Ninety-five percent of the mostly adolescent 107 ill people had Pontiac fever, and the remainder had legionnaires disease. Because the hot tub had been heavily disinfected before analysis by investigators, the results of hot tub water cultures were negative, but the results of PCR for L. pneumophila were positive. As in many outbreaks, a minority (46%) of persons with Pontiac fever had elevated L. pneumophila antibodies.

This otherwise routine Pontiac fever investigation had a remarkable finding: 36% of persons with Pontiac fever had detectable L. pneumophila serogroup 1 antigenuria. Prior studies of urinary antigen testing in Pontiac fever have had very low yields. As might be expected, none of 91 patients in 4 different Pontiac fever outbreaks associated with Legionella species other than L. pneumophila had tests positive for L. pneumophila serogroup 1 antigenuria [4, 5, 12, 18]. Only 4 of the 45 patients with Pontiac fever in 4 different outbreaks associated with L. pneumophila serogroup 1 had positive test results, and all 4 positive test results (4 [22%] of 18 tests) were from outbreaks associated with the Pontiac monoclonal subtype of L.
pneumophila serogroup 1 [10, 11, 19, 20]. The urine antigen test is significantly more sensitive for the detection of Pontiac subtype legionnaires disease than for legionnaires disease due to other monoclonal types of L. pneumophila serogroup 1 [21].

The high frequency of urine antigen positivity in the Oklahoma City Pontiac fever outbreak provides reasonable evidence that this Pontiac fever outbreak was due, in part, to inhalation of live or dead L. pneumophila and storage of urine specimens obtained from patients affected by possible Pontiac fever. If epidemiologic and clinical testing of non–outbreak-associated febrile patients without evidence of pneumonia is not performed to confirm cases and the cause of the outbreak.

Investigation of this Pontiac fever epidemic has provided us with a new tool to help investigate some outbreaks of the disease. Use of the antigen test in the investigation of future Pontiac fever epidemics will help us understand the utility and cost-effectiveness of this test in outbreak investigation. A better understanding of the pathogenesis of the disease awaits the development of an animal model and better tests to detect inhaled endotoxin disease, as well as investigators interested in the disease. Continued collection of data on endotoxin in disease outbreaks will be useful, as will more detailed knowledge of the microbiology and chemical contents of the implicated environmental sources.

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References


