Editorial

Editor's introduction to guest editorial

The risk of infection in the transplant patient is largely determined by the interaction among three factors: the presence of anatomical/technical abnormalities (usually due to surgical misadventures or vascular access issues), the nature and extent of environmental exposures, and the patient's net state of immunosuppression. Recognizing the importance of these factors, particularly the last two of these, one can regard the transplant patient (and other immunosuppressed hosts) as a 'sentinel chicken'; that is, any increased traffic in a variety of potential pathogens will be seen first and foremost in these patients who have been staked out in the swamps of the hospital environment.

Since the first outbreaks of Legionnaires' disease were recognized, it has been clear that transplant patients bore a greater burden of disease than the general population. In addition to *L. pneumophila*, type 1 (which accounts for $>80\%$ of the *Legionella* isolates), the other species of *Legionella* are found more commonly among transplant patients and other immunocompromised hosts.

In this editorial, Drs Singh, Stout, and Yu, who have contributed so much to our knowledge about this group of pathogens, have provided a beautifully crafted synthesis of the diagnostic, epidemiologic, and therapeutic aspects of legionellosis. We are in their debt.

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Guest editorial

Prevention of Legionnaires' disease in transplant recipients: recommendations for a standardized approach

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Legionnaires' disease; *Legionella*; prevention; transplant

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In this issue of *Transplant Infectious Disease*, Fraser et al. (1) describe a case of Legionnaires' disease in a liver transplant recipient. The pneumonia was characterized by the abnormalities considered classical for Legionnaires' disease including hyponatremia, abnormal liver function tests, renal dysfunction, and elevated serum creatinine phosphokinase. These laboratory abnormalities have been found to be significantly more abnormal in patients with Legionnaires' disease than in pneumonias of other etiology, as described in a survey of 13 studies of comparative evaluations of community-acquired pneumonia (2).

The laboratory diagnosis of Legionnaires' disease can be made by culture of the bacterium from a respiratory tract specimen (typically), visualization of the organism by direct immunofluorescence assay (DFA) with polyclonal or monoclonal antibodies, detection of *Legionella* antigen in urine, or demonstration of seroconversion. The most sensitive and specific diagnostic method is culture, followed by the urinary antigen test, DFA, and serology. However, culture requires some experience as well as use of the three-plate culture system using selective media to minimize competing oral flora. Invasive procedures to obtain respiratory tract specimens, such as computed tomography (CT)-guided needle biopsy of the lung, usually are not necessary if the three-plate culture system is used (3).

The laboratory methodologies used by the authors were definitive. *Legionella* was isolated from blood culture by the BACTEC system and the CT-guided lung biopsy also yielded *L. pneumophila*. Blood cultures have been used for isolation of *L. pneumophila* and its occurrence in this case also gives a clue as to the invasiveness of *L. pneumophila*. Similar to pneumococcal pneumonia with its high rate of complications and mortality, *L. pneumophila* can spread to other areas of the body via blood. Legionnaires' disease has a higher mortality than other pathogens of community-acquired pneumonia including the 'atypical' pathogens of *Chlamydia pneumoniae* and *Mycoplasma pneumonia*. The fact that blood

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cultures for *Legionella* are not used in most clinical microbiology laboratories is due to the fastidious nature of the organism. However, Rihs et al. (4) have isolated it from blood cultures; in patients with Legionnaires' disease in whom blood was subcultured to BCYE agar, 38% had positive cultures for *L. pneumophila*.

The serogroup of the *Legionella* isolated from culture was not given in this report, but it was probably not serogroup 1 because the urinary antigen test was negative. *L. pneumophila* serogroup 1 is most commonly associated with Legionnaires' disease and this test is sensitive and highly specific for serogroup 1 only. If *L. pneumophila* serogroup 1 had been the infecting strain, we would have expected the urinary antigen test to still be positive in this patient (even after 4 weeks), because urinary antigen excretion in immunosuppressed patients is prolonged ($\geq$60 days), whereas antigen excretion was $<$60 days in immunocompetent patients (5). Our experience with culture-confirmed cases showed that the duration of antigen excretion in most patients was $<$30 days (6). Serogroup 1 also appears to be more virulent than other serogroups and is more common in the community (7). Non-serogroup 1 species, however, are more common in hospital water distribution systems (8). Thus, *L. pneumophila* non-serogroup 1 infections can often occur in a hospital setting with immunosuppressed hosts (9).

The Fraser et al. (1) case also exemplifies the complicated course of immunosuppressed patients such as transplant patients. Although 10–14 days is now considered the standard duration of therapy for Legionnaires' disease even in transplant recipients, relapse in transplant recipients appeared to be common and therefore a 21-day treatment duration was originally recommended for immunosuppressed hosts (10).

The failure of levofloxacin in the Fraser et al. case is somewhat surprising. A recent study of levofloxacin for community-acquired pneumonia in immunocompetent hosts showed a 0% mortality (11). Mortality rates have steadily declined since the early discovery of Legionnaires' disease when erythromycin and tetracycline were the drugs of choice, particularly for community-acquired disease. However, the mortality rates for hospital-acquired Legionnaires' disease remain high (20–40%) (12). The patient reported by Fraser et al. ultimately was cured with a 21-day course of levofloxacin therapy, although lobectomy had also been performed.

Clinical failures due to resistance of the organism to the antimicrobial agent have not been documented (13). Studies of large numbers of clinical isolates have shown uniform susceptibility to macrolides and quinolones (14, 15). Therefore, the likely cause for persistence of the organism and the need for prolonged therapy in immunocompromised patients is the failure of the host's immune system to assist fully in clearing the infection. The impaired clearance of *Legionella* antigens in urine is presumably due to immunosuppression (5).

Macrolide antibiotics that have a 14-membered lactone ring inhibit the metabolism of tacrolimus by both the hepatic and small intestinal cytochrome P450 enzymes (16, 17). Increased tacrolimus levels with co-administration of erythromycin and clarithromycin have been amply documented in the clinical setting (18–20).

The interaction of azithromycin with tacrolimus is unclear. Azithromycin is a member of the azalide class of antibiotics that differs from erythromycin and clarithromycin in having a 15-membered ring. Oral administration of azithromycin in Sprague–Dawley rats had no effect on cytochrome P450 or NADPH-cytochrome c reductase (21). While there are no studies to date in humans, a possible interaction with an increase in cyclosporine A level was reported anecdotally with the co-administration of azithromycin and cyclosporine A in a transplant recipient (22).

Unfortunately, the laboratory coup of isolating the organism from blood and lung was not fully exploited in the Fraser et al. case, in that the isolation of the organism should have allowed a molecular epidemiologic approach to confirm the source of the organism. This case was considered to be a community-acquired case of Legionnaires' disease. However, it is also possible that the source of the organism might have been the hospital water supply (23). Marrie et al. (24) reported a case of Legionnaires' disease in which colonization of *L. pneumophila* from the water supply of the hospital occurred 63 days prior to development of Legionnaires' disease. Since the patient had been hospitalized just one month prior to admission, it is possible that she may have been colonized by the organism during the first admission and presented with infection one month later subsequent to administration of high-dose corticosteroids. Cultures of the water supply from the patient's home and hospital water would have been most useful, and molecular subtyping of the *Legionella* from the patient and the environment might have identified the source.

We recommend a standardized approach, as has been elucidated by the State of Maryland Department of Health (available at www.Legionella.org), the Allegheny County (Pittsburgh) Health Department Guidelines (also available at www.Legionella.org), and the Centers for Disease Control and Prevention (CDC). The CDC has recommended that hospitals with solid organ and hematopoietic stem cell transplant programs perform periodic culturing for *Legionella* in the potable water supply of the transplant unit as part of a comprehensive strategy to prevent hospital-acquired Legionnaires' disease in transplant units (25, 26). Given the established predilection for Legionnaires' disease in transplant recipients, it would be prudent for all hospitals specializing in transplants to culture their water distribution system, as that is the source for the organism. Numerous hospitals have discovered the presence of unsuspected Legionnaires' disease after initiating a search for cases based on the knowledge that the water supply was colonized with the organism (27). In two Maryland hospitals performing transplants, cases of hospital-acquired Legionnaires' disease were uncovered within weeks of institution of the Maryland guidelines for Legionnaires' disease,

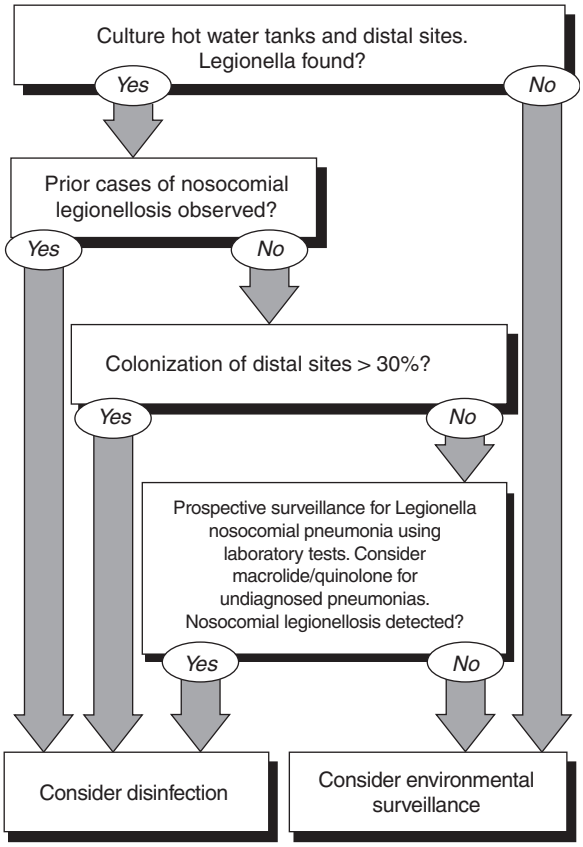

Fig. 1. An approach to disinfection for *Legionella*.

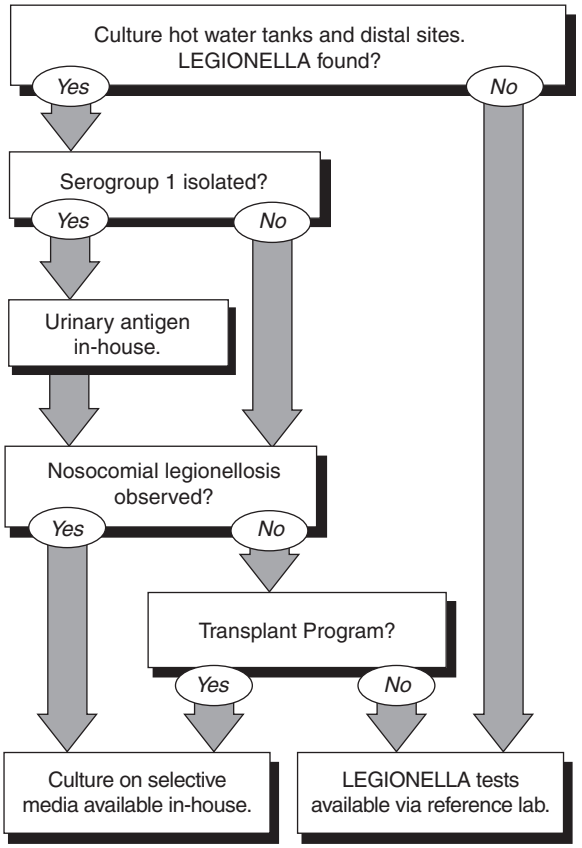

Fig. 2. An approach to laboratory capability for hospitals against *Legionella*.

which mandated culturing of the hospital water supply even if cases had never been discovered.

The Allegheny County Health Department Guidelines (Pittsburgh) approach is given in Fig. 1. Culture of the water supply yielding *Legionella* should immediately raise the index of suspicion that Legionnaires' disease could occur. This would stimulate the hospital microbiology laboratory to adopt *Legionella* laboratory testing in-house, especially culture of respiratory secretions with a three-plate system.

For those hospitals colonized with *L. pneumophila* serogroup 1 in the water supply, the urinary antigen would be an invaluable test and should be obtained on all patients with hospital-acquired pneumonia. As new methodologies have become available, including a commercially available method based on polymerase chain-reaction (PCR), the BD ProbeTec ET (Becton Dickinson, Sparks, MD, USA), rapid and sensitive diagnostic techniques will allow immediate diagnosis with more successful treatment.

Aspiration has been shown to be the major mode of transmission in hospitalized patients (28–30). The policy of banning showers in hospitals colonized with *Legionella* is no longer necessary since numerous case–control studies have shown that showering is not a risk factor. Paradoxically, two studies showed that patients who showered were less likely to contract Legionnaires' disease than controls (28, 31); this occurred because of the indirect effect that patients who shower are ambulatory and less likely to aspirate the organism.

Disinfection of the water supply is now cost-effective. The superheat and flush method has been effective but is very labor-intensive and should only be used to abort an outbreak, since recolonization could easily recur following the superheat and flush. Hyperchlorination proved ineffective and caused corrosion of the plumbing system. Copper silver ionization units have now been shown to be efficacious and cost-effective based on a four-step criteria proposed by Stout and Yu (32). Newer methods including monochloramine and chlorine dioxide are undergoing evaluation, although disadvantages preclude immediate application.

The Allegheny County Health Department Guidelines recommend that when the colonization rate of distal sites within a hospital reaches 30%, disinfection measures should be strongly considered. The 30% threshold was empirically derived; in two hospitals, cases of Legionnaires' disease did not occur until the colonization rate exceeded 30% (33, 34).

Given the extraordinary effectiveness of the newer antibiotics, especially the quinolones, we believe that infection control surveillance to establish the relative risk of Legionnaires' disease is now an acceptable

alternative to immediate disinfection of the water distribution system. Disinfection can be postponed until the clinical problem has been clearly elucidated. If laboratory methodologies are available in-house, clinicians can obtain the results expeditiously. Quinolones can be given empirically for hospital pneumonias of uncertain etiology. If infection control surveillance results in a large number of cases of Legionnaires' disease being uncovered, then disinfection methods could be initiated.

Because Legionnaires' disease can be acquired through any water source, including that of work places and homes, we also recommend that transplant recipients no longer drink tap water. Transplant recipients should instead boil their water, cool it, and store it for drinking. This suggestion is not as radical as it seems, since patients with human immunodeficiency virus (HIV) have already been advised to boil their water as a precaution against waterborne pathogens (e.g., *Cryptosporidium*) (35).

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