

# Legionnaires' disease: a rational approach to therapy

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**Optimal therapy against *Legionella* infection is based on agents with a high intrinsic activity, an appropriate pharmacokinetic and pharmacodynamic profile (including the ability to penetrate phagocytic cells), a low incidence of adverse reactions and an advantageous cost–efficacy relationship. Newer macroazalides and fluoroquinolones are among the first-line therapies and in severe infections, particularly those occurring in immunocompromised patients, azithromycin and later fluoroquinolones are the agents of choice. Delay in the onset of adequate therapy is a key factor associated with a poor outcome. Thus, all patients with pneumonia associated with respiratory failure, shock or underlying disease causing severe immunodeficiency should initially receive an agent active against *Legionella* spp., at least while the aetiology remains unknown. Adjunctive measures improve outcome in critically ill patients. In intubated patients with delayed resolution, superinfection by *Pseudomonas aeruginosa* or co-infection caused by other pathogens should be excluded.**

Keywords: Legionnaires' disease, therapeutic approach

## Role of *Legionella* spp. in lower respiratory tract infection

*Legionella* spp. are identified consistently as among the most common causative agents of severe community-acquired pneumonia (CAP).<sup>1</sup> Their role in more benign forms of CAP remains controversial. Differences in the patient subsets studied, inclusion criteria and diagnostic methodology, may partly explain apparent discrepancies. In patients with more severe symptoms, requiring a greater degree of hospital care, the percentage of *Legionella* spp. isolates increases, ranking second only to the pneumococcus in many studies of the aetiology of severe CAP. A recent review of 41 CAP studies identified *Legionella* spp. as the causative pathogen in 1.9% of ambulatory patients, 4.9% of hospitalized patients and 7.9% of those requiring admission to the Intensive Care Unit (ICU).<sup>2</sup> However, during minor, sometimes unsuspected epidemics, Legionnaires' disease may represent a much greater proportion of CAP requiring admission to hospital and the ICU.<sup>3</sup> Nosocomial legionellosis may occur in epidemics, but the detection of most such outbreaks usually infers the existence of prior unsuspected sporadic nosocomial cases.

The possibility of legionellosis is easily overlooked unless specialized laboratory diagnostic methods are applied,<sup>4</sup> and its true incidence is probably underestimated, as many *Legionella* spp. and serogroups cannot be identified accurately by contemporary commercial microbiological tests. The number of newly identified species is continually increasing.<sup>5</sup> Currently, there are at least 48 *Legionella* species with 70 serogroups, and some species, initially thought non-pathogenic, are now associated with human disease.<sup>5,6</sup>

## Other *Legionella* spp. and *Legionella*-like amoebal pathogens

The place of *Legionella pneumophila* serogroup 1 as the pre-eminent pathogen has been recently confirmed by an international collaborative survey of 508 culture-proven cases of sporadic, community-acquired legionellosis.<sup>7</sup> *L. pneumophila* constituted 91.5% of the isolates and serogroup 1 (84.2%) predominated. Interestingly, *Legionella longbeachae*, often associated with exposure to contaminated potting soil mixes, constituted 30.4% of isolates in Australia–New Zealand. These culture-derived results, from many countries, are probably representative of the true worldwide distribution, as

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the number of isolates was large and all corresponded to sporadic, community-acquired cases.

Others have highlighted the potential role of *Legionella* spp. that are different from *L. pneumophila*, and of *Legionella*-like amoebal pathogens (LLAP), as causative agents of pneumonia, both in hospitals and the community.<sup>8–10</sup> LLAP refers to a subset of bacteria that grow exclusively within amoebae and that are phylogenetically close to *Legionella* spp. Their numbers are increasing progressively and, despite specificity concerns, serological studies suggest many may be potential causes of human infection, principally as co-infectious agents. Although their role appears minor, it may have therapeutic implications if, for example, fluoroquinolone resistance in isolates of *Parachlamydia acanthamoeba* is confirmed.<sup>11</sup>

## Epidemiology and pathogenesis

Many cases of legionellosis relate to exposure to contaminated water.<sup>1,5</sup> The precise mode of transmission remains controversial, but it seems clear that both aspiration of colonized water and inhalation of aerosols are involved in acquisition.<sup>5</sup> Attention has been drawn to the risk of acquisition via contamination of domestic aquatic reservoirs.<sup>12</sup> Knowledge is increasing of the relationship between amoebae, biofilms, *Legionella* spp., LLAP and other microorganisms that can also survive and propagate inside free-living amoebae,<sup>5</sup> for example those associated with aquatic environments—such as *Acanthamoeba* spp., and cooling towers. This interrelationship of amoebae and *Legionella* spp. may have clinical and therapeutic implications since intra-amoebal growth may result in strains with increased virulence and antibiotic resistance.<sup>13–15</sup>

Detailed comment on pathogenic factors and virulence determinants is outside the scope of this article, but has been extensively reviewed.<sup>16–18</sup>

## Risk factors

Factors that render patients at higher risk of acquiring *Legionella* spp. infection comprise advanced age, underlying comorbidity, including alcoholism, chronic obstructive pulmonary disease and cigarette smoking, and either corticosteroid or other forms of immunosuppressive therapy.<sup>1,5</sup> The link between smoking and *Legionella* spp. infections is now better understood,<sup>19</sup> and a few *in vitro* studies support a link between cocaine abuse, marijuana smoking and Legionnaires' disease.<sup>20</sup>

Transplant recipients, including renal and non-renal transplants, are highly susceptible to infection. In some series of infections in liver transplant recipients, *Legionella* spp. are among the predominant pathogens,<sup>21</sup> perhaps associated with

simultaneous splenectomy for associated hypersplenism.<sup>22</sup> AIDS patients may also be at increased risk.

However, Legionnaires' disease—even severe cases—may occur in previously healthy subjects and the absence of underlying disease should not be a reason to exclude the diagnosis.<sup>1</sup> In one series of hospitalized patients, Legionnaires' disease occurred more frequently in middle-aged men without predisposing factors, excepting that of excess alcohol intake.<sup>3</sup> Another study of non-severe CAP found that all cases of Legionnaires' disease corresponding to Fine groups 2 and 3 occurred in patients aged <50 years without comorbidity.<sup>23</sup> Even in the nosocomial setting, up to 6% of cases occurred in the absence of significant underlying illness.<sup>24</sup> Iron overload has recently been suggested as a potential risk factor for severe legionellosis.<sup>25</sup>

## Clinical features

Legionellosis may range from mild respiratory illness to fulminating pneumonia.<sup>1,5</sup> The 'benign' variant, Pontiac fever, has also been associated with rare, severe complications, such as encephalitis.<sup>26</sup> Numerous comparative studies of both community-acquired and nosocomial legionellosis show the clinical, radiological and laboratory features to be non-specific.<sup>1,3,5,24,27</sup> Even where differences between legionellosis and other causes of CAP are shown, their clinical relevance can be minimal. For example, an excellent comparative study demonstrated a few statistically significant factors differentiating legionellosis from other forms of CAP: specifically, creatinine kinase level increase and diarrhoea were suggestive of legionellosis.<sup>3</sup> However, the majority (68% and 75%, respectively) of the patients had neither feature and their clinical relevance is, therefore, doubtful. Failure of prior domiciliary  $\beta$ -lactam therapy of CAP should arouse suspicion of legionellosis. In dual (polymicrobial) infections, clinical manifestations caused by co-infecting organisms may dominate presentation.

The allegedly typical progression of chest X-ray infiltrates, despite adequate therapy, can also be misleading. Clearly, there is an association between the extent of radiological involvement and the onset of respiratory failure.<sup>28</sup> However, personal experience of patients receiving effective treatment from the onset indicates that radiographic progression of infiltrates is limited to ~30%.<sup>29</sup>

## Laboratory diagnosis

Table 1 summarizes the diagnostic methods available. *Legionella* antigen detection in urine samples, owing to its simplicity, high sensitivity and specificity, has been the most significant breakthrough in diagnosis.<sup>4</sup> Since urinary antigen tests do not detect infections caused by all *Legionella* spp.,

**Table 1.** Non-invasive tests for detection of *Legionella*

Tests	Sensitivity (%)	Specificity (%)	Time required
Sputum culture	10–80	100	3–7 days
Serology	40–70	95–99	1–6 months
DFA of sputum	33–70	95–99	2–4 h
Urinary antigen assay			
ELISA	>90	99–100	2–3 h
IC	>90	99–100	15 min if NCU
PCR (serum, urine, respiratory samples)	33–70	98–100	2–4 h

DFA, direct fluorescent antibody staining; IC, immunochromatography: 2 h more if urine is concentrated as advised; NCU, non-concentrated urine.

specific culture is always indicated, even if antigen testing proves negative. In addition, culture isolates are crucial in identifying environmental sources of the disease, and confirm that culture is appropriate in those with a positive urinary antigen test. Furthermore, negative antigen tests do not exclude legionellosis with 100% accuracy and, thus, should not prompt discontinuation of specific antibiotic therapy when clinical and epidemiological considerations dictate otherwise. Recently, an association between clinical severity and test sensitivity was demonstrated in a Dutch outbreak.<sup>30</sup> It is noteworthy that this epidemic remained unrecognized for many days and that, during this time, initial empirical therapy was not invariably appropriate. Urinary antigen test results are not generally influenced by several days of prior antibiotic therapy, although a risk of false-positive results in patients receiving anti-thymocyte treatment, or in those with rheumatoid-like factors in urine, has been reported.<sup>31</sup>

### Prognostic factors

Mortality rate is influenced by severity of clinical presentation, immune status, source of infection—either community-acquired or nosocomial—and the initial empirical choice of chemotherapy. Early, effective therapy plays a crucial role in outcome, at least in more severe disease.<sup>32–36</sup>

The most consistently identified prognostic factors in legionellosis are: (i) APACHE II score >15 at admission; (ii) requirement for endotracheal intubation; (iii) advanced age; (iv) renal disease; (v) malignancy; (vi) immunosuppression; (vii) infection by *L. pneumophila* serogroup 6; and (viii) delay in administration of appropriate treatment.

Some have suggested that rhabdomyolysis, although of low prevalence, is also associated with a poor prognosis.<sup>37</sup> In severe rhabdomyolysis, secondary renal involvement may be the primary factor associated with higher mortality.

## Treatment

### General considerations

A decade ago we published recommendations for therapy of Legionnaires' disease.<sup>38</sup> Since the early 1990s, the treatment of choice has shifted from erythromycin to newer macroazalides and fluoroquinolones.<sup>1,39–41</sup> These antibiotics combine high intrinsic potency with enhanced ability to penetrate and concentrate within phagocytic cells. Randomized clinical trials demonstrating differences between the effectiveness of antibiotic classes in legionellosis are, however, unlikely ever to be performed.<sup>39</sup> Thus, most treatment recommendations are based on informed clinical experience and evidence from experimental *in vitro* cellular and animal models.<sup>38,41</sup> However, conclusions derived from experimental systems may not translate to human disease and small differences, even when demonstrated, may not be clinically relevant.

Potentially misleading results from *in vitro* cellular models have been reported over the past 25 years. Differences in the media, inoculum size, types of host cells and strain variations may explain some of the controversies arising from different *Legionella* susceptibility testing studies.<sup>1,38–43</sup> Animal model systems are probably superior to cellular studies, as they reflect differences in more relevant parameters—such as survival rate, bacterial clearance and the degree of lung inflammation and fibrosis. In animal models, bacterial clearance is more efficient with the potent, newer fluoroquinolones than with erythromycin.<sup>44–46</sup> Among the macroazalide group, azithromycin has been reported to be superior to clarithromycin or erythromycin in many cell models and most animal experimental models.<sup>47–52</sup>

There are striking differences in the influence of different antimicrobials on lung inflammation. In the animal model, the least inflammation is found in association with azithromycin therapy, moderate inflammation with the fluoroquinolones and the greatest with erythromycin. Moreover, in the macrophage model, both azithromycin and fluoroquinolones may induce either prolonged or irreversible inhibition of *Legionella* intracellular growth, even after drug removal.<sup>47,53–57</sup>

Research on agents potentially active against *Legionella* is not limited to conventional antibiotics. For example, *in vitro* or experimental activity is demonstrated by agents from natural products, e.g. licochalcone A (derived from Chinese liquorice roots) and epigallocatechin gallate—a major group of tea catechins.<sup>19,58</sup>

### Recommended antibiotic treatment

The initial empirical therapeutic approach to severe cases of CAP should include an antimicrobial agent effective against *Legionella* spp.<sup>59</sup> In addition, there is a clear distinction between recommendations appropriate to normal hosts and those for immunocompromised patients.<sup>39,41</sup> Most cases of

legionellosis develop in immunocompetent patients as a mild infection and many resolve with any macroazalide, fluoroquinolone or tetracycline.<sup>1,38,39</sup>

Oral macroazalide therapy has proven effective in many outpatient studies of mild-to-moderate disease.<sup>38</sup> Erythromycin, clarithromycin, azithromycin, roxythromycin, josamycin, midecamycin and dirithromycin have all been found satisfactory in such patients, and similar results apply to non-macrolide options, such as ciprofloxacin, co-trimoxazole and tetracyclines.<sup>38</sup> The newer fluoroquinolones offer moderately better intrinsic activity against *Legionella* than their predecessors.<sup>39–42,46,49,55–57,60</sup> Trovafloxacin and sparfloxacin were substantially more potent than ciprofloxacin, but were suspended/withdrawn from general use because of potential toxicity. Preliminary data indicate that telithromycin is a further possibility,<sup>61</sup> but there is, so far, limited clinical evidence confirming ketolidides as first-line therapy, and the lack of an intravenous formulation (of telithromycin) is a shortcoming in hospitalized patients. The activity of linezolid is clearly marginal, but quinupristin–dalfopristin may have mild, clinically useful activity.<sup>52,57</sup> Rifampicin is active against *L. pneumophila*, but monotherapy risks induction of resistance.<sup>62</sup>

Table 2 summarizes a treatment protocol for patients with Legionnaires' disease requiring admission to hospital. Delay in adequate therapy is associated with a poor outcome and the non-availability/licensing of intravenous formulations of some agents in all countries, for example of clarithromycin in the USA or azithromycin in parts of Europe, is a deficiency in this regard. Agents with available parenteral formulations are therefore preferred. Some authorities recommend an initial loading (double) dose<sup>1</sup> for severe disease and immunocompromised patients. The recommendation of drugs that are

most active in experimental models, i.e. azithromycin and new fluoroquinolones, is targeted at improving bacterial clearance and, possibly, reducing relapse.<sup>1,39,41,63</sup> A further advantage is the reduced potential for drug interactions, particularly with immunosuppressive agents.<sup>64</sup>

### Combination therapy

Combined therapy has mostly been used in severe unresponsive disease.<sup>38,63</sup> There is no convincing evidence of its effectiveness<sup>40,41</sup> and combinations may risk additional toxicity and drug interactions. However, in deteriorating patients unresponsive to standard monotherapy, addition of further potentially active antibiotics is appropriate.<sup>40</sup> In cellular systems, rifampicin appears to add little to fluoroquinolone activity, but in the guinea pig model it may be beneficially combined with macrolides such as erythromycin.<sup>38</sup> Nevertheless, concern regarding potential toxicity and significant metabolic alterations resulted in reduced use of rifampicin once more active agents, e.g. azithromycin and levofloxacin, became available. In addition, jaundice and reversible hyperbilirubinaemia occurred in a high percentage of patients following rifampicin use in severe legionellosis.<sup>65</sup> If rifampicin is chosen for combination therapy, a short course (<5 days) seems most prudent.<sup>65</sup>

Some *in vitro* data support the combination of macroazalides with newer fluoroquinolones.<sup>66</sup> Once more, supportive clinical evidence is lacking, although the anti-inflammatory activity of macroazalides and the bactericidal activity of new fluoroquinolones may influence choice in severe cases. In experimental murine fungal pneumonias, newer fluoroquinolones also exert favourable immunomodulating effects<sup>67</sup>—a possible additional benefit in legionellosis. If a macroazalide/fluoroquinolone combination therapy is chosen, possible toxicity as the result of interactions with drugs handled by the CYP enzymes, e.g. theophylline, should be anticipated. However, the overall toxicity potential compares favourably with rifampicin combinations.

### Duration of therapy

Clinical judgement should be augmented by assessment of the following factors when deciding the duration of therapy: (i) prior immune status; (ii) severity of clinical presentation; (iii) presence of suppurative, extrapulmonary complications; (iv) initial therapeutic delay; (v) pharmacokinetic and pharmacodynamic profile of the chosen antibiotic; and (vi) response to initial therapy.

In mild-to-moderate cases in immunocompetent patients with a rapid response to treatment, a 10 day course of therapy is probably sufficient. In the more benign forms of the infection, a 5 day course of azithromycin—even 3 days in outpatient series of mild disease—may be effective<sup>68</sup> and could reduce costs. However, in patients with significant underlying

**Table 2.** Preferred therapy for hospitalized patients with Legionnaires' disease

Antimicrobial agent	Dosage <sup>a</sup>
Macroazalides	
azithromycin <sup>b</sup>	500 mg every 24 h
clarithromycin	500 mg every 12 h
Tetracyclines	
doxycycline	100 mg every 12–24 h
Fluoroquinolones	
levofloxacin <sup>b</sup>	500 mg every 24 h
moxifloxacin <sup>b</sup>	400 mg every 24 h
ciprofloxacin <sup>c</sup>	400–750 mg every 12 h

<sup>a</sup>Administered either intravenously or by mouth.

<sup>b</sup>Recommended in the more severe cases, particularly in the immunocompromised.

<sup>c</sup>Dosage may be increased up to 400 mg every 8 h in intubated patients.

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ing comorbidity, invasive disease and either multisystem illness or immunodeficiency, a 3 week course of treatment with either fluoroquinolones or macrolides (other than azithromycin) is necessary to avoid risk of relapse.<sup>1,38–41,69–71</sup>

There appear to be no studies that specifically address the issues of switch therapy and early discharge from hospital. Recommendations published for CAP in general are probably similarly valid in legionellosis.

### Extrapulmonary manifestations

In contrast to common prodromal features, such as myalgia and mental confusion, these are infrequent, later manifestations, which tend to present in immunocompromised patients and are rarely observed in normal individuals.<sup>28,72–74</sup> When extrathoracic features predominate, the diagnosis of pneumonia may be overlooked and appropriate treatment delayed. Extrathoracic localizations of *Legionella* spp. are well documented<sup>72,74</sup> and include: (i) cardiovascular: myopericarditis, endocarditis and aortic graft involvement; (ii) neurological: encephalitis (which may mimic herpes simplex encephalitis), brain abscess and cerebellar ataxia; (iii) digestive: colonic—mimicking ulcerative colitis, pancreatitis, digestive tract abscess, liver involvement and splenic rupture; and (iv) miscellaneous: acute renal failure, interstitial nephritis, wound infection, renal abscess, cellulitis, thrombocytopenia and disseminated intravascular coagulation (DIC).

Longer-term effects may persist after acute infection. Following an outbreak in the Netherlands, the incidence of post-traumatic stress disorder was 15% and general symptoms among survivors included fatigue (75%), neurological symptoms (66%) and neuromuscular symptoms (63%), which persisted for up to 1.5 years after diagnosis.<sup>75</sup> In addition to management considerations, such findings have profound socio-economic implications.

### Mixed (polymicrobial) infection

The possibility of polymicrobial infection should not be overlooked, especially in immunocompromised patients.<sup>76–78</sup> Various mixed infections have been reported.<sup>76–82</sup> Failure to detect a component of polymicrobial infection may cause undesirable delay in appropriate therapy and fatalities can follow missed diagnosis. Figure 1 proposes an algorithmic approach to severe non-resolving legionellosis. PCR, a reliable and rapid technique for detection of *Legionella* spp. and other pathogens in clinical samples and lung tissue, holds potential promise for the identification of polymicrobial infections, although it remains, to date, research-based.<sup>83,84</sup> Open lung biopsy (in ventilated patients with respiratory failure) has a low morbidity and mortality when performed by skilled surgeons,<sup>85</sup> but video-assisted thoracic surgery is an alternative in less severe cases.<sup>86</sup> The following pathogens

have been identified as causing dual infection with *Legionella* spp., in culture-based studies:<sup>76–82</sup>

Aerobic and anaerobic bacteria: *Streptococcus pneumoniae*, *Proteus mirabilis*, *Staphylococcus aureus*, *Escherichia coli*, *Prevotella intermedia*, *Enterococcus faecium*, *Enterobacter cloacae*, *Klebsiella pneumoniae*, *Haemophilus influenzae*, *Neisseria meningitidis*, *Streptococcus mitis*, *Listeria monocytogenes*, *Nocardia* spp.

Dual infections by differing *Legionella* spp. and different serotypes of *L. pneumophila* have been reported, especially in the setting of lung abscess

*Mycobacterium tuberculosis*

Viruses: herpesvirus, influenza virus, cytomegalovirus

Fungi: *Aspergillus*, *Cryptococcus*, *Pneumocystis jiroveci*

Other pathogens have been serologically incriminated in polymicrobial infection, e.g. *Chlamydia pneumoniae*, *Mycoplasma pneumoniae* and some viruses. In polymicrobial pneumonia complicating near-drowning episodes, *Legionella* spp. have occasionally been recognized.<sup>87</sup>

### *Legionella* spp. and acute exacerbations of COPD

Positive *Legionella* spp. serology may occasionally be obtained from patients with acute exacerbations of COPD (AECOPD) and a potential aetiological role has been suggested.<sup>88</sup> However, the evidence is based on serological methods of questionable specificity. There is little evidence supporting Legionellae in the aetiology of AECOPD<sup>89</sup> and much to the contrary. *Legionella* spp. have never been isolated in studies on AECOPD using culture methods, even when direct endo-bronchial samples are obtained via invasive procedures.

In the last 25 years, pathogenetic research has shown clearly that the role of *Legionella* spp. is as an aetiological agent of, primarily, intracellular macrophage infection, with the possible development of pneumonia or, rarely, Pontiac fever, but not of bronchitis itself.<sup>17,18</sup>

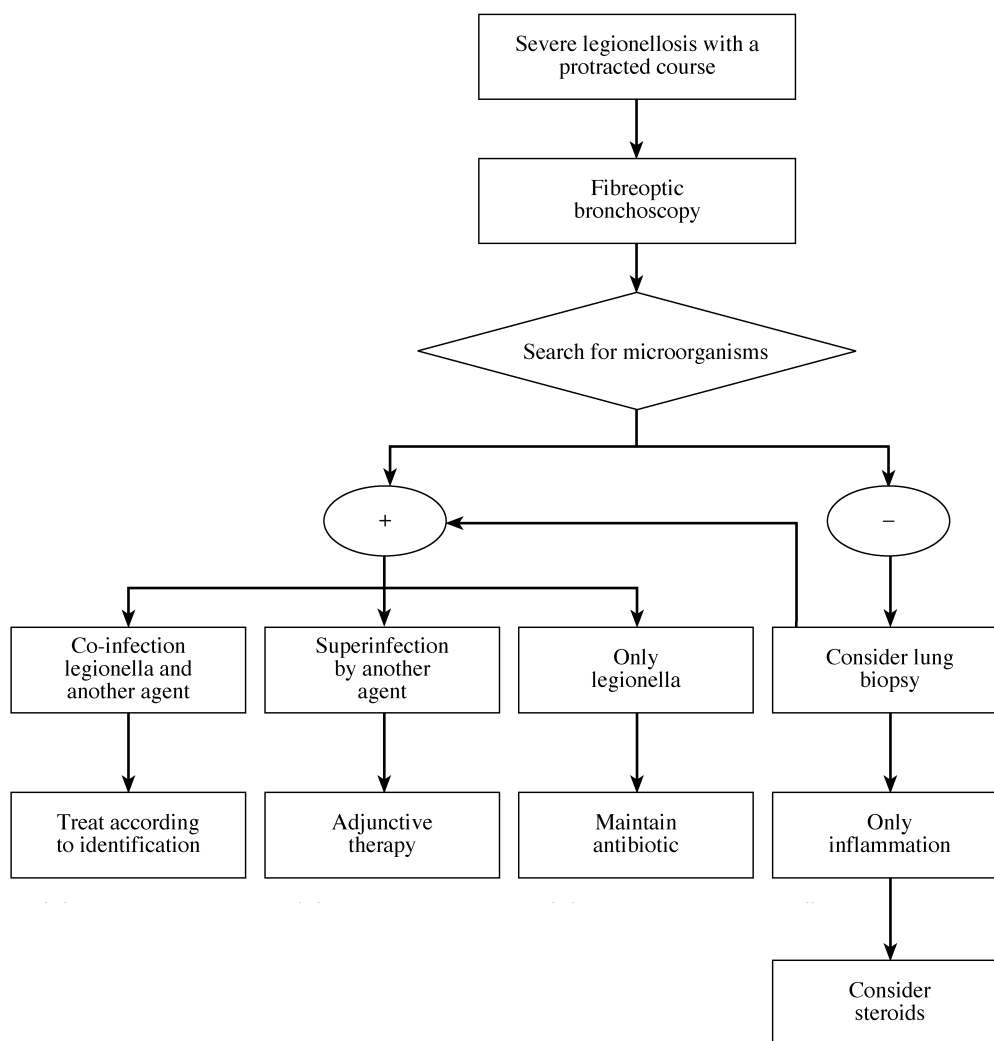
Serological diagnosis lacks specificity and various cross-reactions have been reported.<sup>59</sup> In a low-prevalence disease such as legionellosis, false-positive results are a significant risk.

During outbreaks, exposed individuals who seroconvert either remain healthy or develop legionella pneumonia.<sup>90</sup>

Consequently, there is no current justification for specific treatment, even in AECOPD patients with positive serology.

### Legionellosis and DIC

Complement and platelet activation in severe *Legionella* infection may be associated with clotting abnormalities, significant thrombocytopenia and the formation of platelet microvesicles (not detected by conventional cell counters).<sup>73</sup> DIC, uncommon even in severe legionellosis—except in those with established endotoxic shock—requires conven-



**Figure 1.** Proposal for algorithmic approach to management of intubated patients with non-resolving legionellosis.

tional therapy. Most cases have been reported with non-*L. pneumophila* species, especially *L. longbeachae*. Haemophagocytic syndrome was reported as a complication of severe legionellosis.<sup>91</sup> The treatment of choice has not been established, but anecdotal reports suggest a possible place for intravenous immunoglobulin therapy. Endotoxin elimination, using continuous haemofiltration or exchange transfusion, is under evaluation in severe legionellosis with refractory hypoxaemia and DIC.<sup>92,93</sup>

#### Corticosteroid therapy

Prior corticosteroid therapy is a risk factor for severe legionellosis, but, therapeutically, may be life-saving in adult respiratory distress syndrome (ARDS) and in patients with severe, protracted disease, characterized by either proliferative or interstitial inflammatory responses in the lung.<sup>1,59</sup> These have included bronchiolitis obliterans, organizing pneumonia,

various interstitial pneumonias and follicular bronchiolitis.<sup>94</sup> However, legionellae were not identified in lung tissue from these subjects and the value of corticosteroids, when such inflammatory processes co-exist with active infection, remains unclear. Their administration in patients with legionellosis may favour either progression or relapse and their use requires great caution.

#### Interferon

Interferon- $\gamma$ , a potent activator of macrophages, may enhance the killing ability of phagocyte cells against *Legionella* spp.<sup>95</sup> Murine models of non-lethal, experimental legionellosis show that exogenous administration of interferon- $\gamma$ , through intrapulmonary adenovirus-mediated gene therapy, may induce enhanced killing of intracellular *Legionella* organisms.<sup>96</sup> In the same experimental system, transient transgenic expression of interleukin-12—an inducer of interferon- $\gamma$ —

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also resulted in a modest improvement in the pulmonary clearance of *L. pneumophila*. The clinical implications of these findings in man remain unknown.

### Specific conditions

#### *Pregnancy and paediatric legionellosis*

Pregnant women are not at increased risk of legionellosis, but many cases have been reported during pregnancy and pose an increased risk of premature delivery.<sup>97</sup> Perinatal and paediatric legionellosis is uncommon and usually limited to the nosocomial setting.<sup>98</sup> During pregnancy, macrolides are the first-line treatment. Erythromycin and azithromycin are both recognized as posing no risk of fetal damage by the US FDA. A significantly higher rate of spontaneous abortion occurs with clarithromycin in pregnancy, although there was no significant difference in the rate of fetal malformation.<sup>99</sup> A possible association between pre-natal erythromycin therapy and infantile pyloric stenosis has not been confirmed, but may apply to other macrolides (odds ratio 2.77).<sup>100</sup> Therefore, erythromycin is recommended for mild-to-moderate disease: azithromycin should be reserved for severe legionellosis in pregnancy.

#### *Recurrent or persistent infection*

In pneumonia caused by *Legionella* spp., neither incomplete/delayed clinical resolution nor relapse has yet been demonstrated to be the result of development of resistance to antimicrobials.<sup>101,102</sup> Concerns over the potential appearance of resistance when rifampicin is administered alone relate to *in vitro* studies and have not been confirmed in animal models.<sup>62</sup>

Unsuspected purulent collections, e.g. lung abscess and empyema, causing persistent symptoms, should be investigated appropriately; dual infections should be excluded and, in delayed resolution, superinfection by *Pseudomonas aeruginosa* or other pathogens should be suspected early.<sup>103</sup> In immunocompromised patients, for example with endocarditis, more prolonged treatment may be required.

### Prevention

*Legionella* spp. are ubiquitous in the environment. However, the reported incidence of both community and nosocomially acquired Legionnaires' disease is variable—a sporadic pattern interspersed with small outbreaks and localized epidemics. *Legionella* spp. colonization of hospital (and other) water supplies should be investigated and, when encountered, eradicated to prevent nosocomial acquisition.<sup>104</sup> Silver-copper ionization appears to be a more effective and feasible method of eradication when compared with either chlorine dioxide treatment or maintenance of hot water tank temperatures >55°C. Measures are also required to prevent

contamination of reservoirs located in systems able to generate aerosols, such as cooling towers. Such treatments should be either continuous or frequent as re-colonization occurs rapidly.

### Immunoprophylaxis

Despite preliminary studies in experimental models, an effective *Legionella* vaccine is still lacking.<sup>105</sup>

### Chemoprophylaxis

Legionellae are not normally carried in the throat or airways in the absence of disease.<sup>106,107</sup> However, a recent PCR-based study identified *L. pneumophila* in 37 sputum or bronchial aspirates from 298 samples taken from patients before organ transplantation.<sup>108</sup> These results are preliminary, and possible confounding factors include the risk of auto-contamination associated with PCR techniques and the lower specificity of direct fluorescent antibody tests. Thus, caution is appropriate prior to acceptance that *Legionella* spp. may colonize the respiratory tracts of such highly selected population subsets, who might thus potentially justify prophylaxis.

In practice, priority should be given to localization of the source and eradication of contaminating *Legionella* spp. However, transitory chemoprophylaxis of high-risk populations, either with macroazalides, co-trimoxazole or fluoroquinolones, can be effective.<sup>109–113</sup> Azithromycin has an advantageous pharmacokinetic and pharmacodynamic profile, and is possibly the best option for this strategy. Its prophylactic efficacy is recognized in both *M. pneumoniae* and *C. pneumoniae* infections.<sup>114</sup> However, prior prophylaxis does not preclude subsequent development of legionellosis, especially if patient compliance is uncertain.

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