Problem pathogens: paediatric legionellosis—implications for improved diagnosis

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Legionnaires' disease is an established and frequent cause of pneumonia in adults but is thought to be a rare cause in children. We reviewed the medical literature for cases of Legionnaires' disease in children and analysed the epidemiology, clinical characteristics, and treatment. 76 cases of legionella infection in children were identified. In 56%, diagnosis was made with culture methodology. 46% were community-acquired infections. 51·5% were under 2 years of age. 78% of the patients had an underlying condition such as malignancy. Fever, cough, and tachypnoea were the most common symptoms. The overall mortality rate was 33% and was higher in immunosuppressed children and in children younger than the age of 1 year. Patients who were treated empirically with anti-legionella therapy had a notably lower mortality rate compared with patients on inappropriate therapy (23% *vs* 70%). In 88% of hospital-acquired cases, an environmental link to potable water colonised with legionella was identified. We found no clinical features unique to Legionnaires' disease in children that would allow differentiation from pneumonia due to other respiratory pathogens. Awareness of legionella as a potential cause of paediatric pneumonia is particularly important because infection can be severe and life threatening and antimicrobial therapy often used for empirical therapy in children is not effective against legionella. In any case of pneumonia unresponsive to antibiotics, Legionnaires' disease should be considered and specific diagnostic tests to verify this diagnosis should be done. As legionella diagnostic tests become more widely applied, we predict that legionellosis may appear as an emerging infectious disease in children.

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Introduction

Legionnaires' disease is considered a rare cause of community-acquired pneumonia in children. Seroepidemiological studies in children have shown variable results with raised titres of legionella antibody ranging from 2% to 52%.[1,2] A prospective study found raised titres for *Legionella pneumophila* in 52% of children without clinical signs for infection.[3] The authors concluded that "*L pneumophila* is not a common cause of acute respiratory disease in early childhood in the study area but that children are frequently exposed to the organism."[3] Diagnosis based only on serological tests for which the sensitivity and specificity is uncertain is a major drawback for these earlier studies in children. We reviewed the literature of paediatric legionellosis. However, we adopted rigorous criteria for the diagnosis of legionellosis in the cases to be included in this review. The evolutionary course of discovery of Legionnaires' disease in children seems to parallel that of adults. We suggest an approach that might uncover occult cases of Legionnaires' disease in children to allow earlier treatment and, possibly, prevention.

Paediatric cases of legionella infection

We identified 76 cases of legionella infection in children that fulfilled our inclusion criteria.[1–56] Diagnosis was made with legionella culture methodology in 45 (59%) of these cases; culture was the only diagnostic method that was positive in 23 (30%) cases. Seroconversion and direct fluorescent antibody (DFA) assay were also frequently used alone or in combination with other methods (table 1 and table 2). Most reports were from North America and Europe (table 3). Of the 76 cases, serogrouping and speciation was available for 46: 22 were caused by *L pneumophila* serogroup 1, 15 by *L pneumophila* serogroup 6, one by *L pneumophila* serogroup 3, one by *L pneumophila* serogroup 8, three by *Leigionella dumoffii*, three by *Legionella micdadei*, and one by *Legionella gormanii*.

35 cases (46%) were community-acquired infections. Of the 68 patients with age recorded, 26 (38%) were under the age of 1 year; 41 (61%) were in boys. 59 (78%) of the patients had an underlying condition including malignancy, transplantation, corticosteroid usage, congenital immunodeficiency, prematurity, and underlying respiratory diseases (table 4). Of note, of the 17 patients who had no underlying disease, seven (41%) were under the age of 1 year.

Fever and cough were the most common symptoms in children with legionella infection (table 5). Tachypnoea, hypoxia, and abnormal lung examination were the most common signs in patients; 13 patients needed mechanical ventilation. The most common laboratory findings were leucocytosis (>15 000 white blood cells per mL; n=15),

Methods	Number of positive tests	Frequency
Culture	45	59%
Serology	32	42%
DFA	25	66%
Urine antigen	4	5%
PCR	3	4%

DFA=direct fluorescent antibody. The tests total greater than 76 because some patients had multiple tests positive.

Table 1: **Laboratory testing for *Legionella* spp in 76 paediatric patients with Legionnaires' disease**

Methods	Number of positive tests	Frequency
Culture only	23	30%
Culture and serology	5	7%
Culture and DFA	14	18%
Culture, DFA, and serology	2	3%
Culture and urine antigen	1	1%
DFA only	4	5%
Serology only*	18	24%
DFA and serology	3	4%
DFA, serology, and urine antigen	1	1%
DFA, serology, urine antigen, and culture	1	1%
PCR and serology	2	3%
Urine antigen only	1	1%
PCR only	1	1%
Total	76	100%

DFA=direct fluorescent antibody. *Fourfold rise of antibody titre after onset of pneumonia.

Table 2: **Laboratory tests subclassified for 76 children**

left shift (>1500 bands per mL; n=13), leucopenia (<5000 white blood cells per mL; n=10), increased C-reactive protein or erythrocyte sedimentation rate (n=6), coagulopathy (n=5), and abnormal liver function tests (n=3). Pulmonary infiltrates were found in 61 (97%) of cases when chest radiography findings were reported, and pleural effusion was common, being found in 19 (30%) cases (table 6).

Underlying conditions were notably more common in children with hospital-acquired versus community-acquired infections (100% *vs* 57%). The mortality rates were higher in hospital-acquired Legionnaires' disease compared with community-acquired Legionnaires' disease (41% *vs* 23%) (table 7).

In 35 (46%) cases, environmental investigations were done. In 26 (74%) of these cases, an environmental link to potable water was identified. Most investigations were in hospital-acquired infections, and hospitals were more likely to yield legionella than homes (table 7).

The mortality rate was 33% (25/76) overall and was higher in immunosuppressed patients than in immunocompetent patients (42% [21/50] *vs* 15% [4/26], respectively). Mortality was also high in children younger than 1 year of age: 50% (14/28) compared with 25% (10/40) in children older than 1 year. Patients who were treated empirically with anti-legionella therapy had a substantially lower mortality rate compared with patients on inappropriate therapy (24% [9/21] *vs* 76% [29/34]; table 8).

Discussion

Legionnaires' disease in adults is now an established and frequent cause of both community-acquired and hospital-acquired pneumonia.[57,58] However, from the 1980s to the early 1990s, Legionnaires' disease was considered a rare and exotic disease usually identified with sporadic outbreaks. As diagnostic methods improved and were more commonly used, cases of Legionnaires' disease increased.[59]

Pneumonia is a common infection in children, but few reliable clinical or radiological features exist that allow differentiation among the various respiratory pathogens. The clinical presentation and natural course of Legionnaires' disease in children is not clear, since studies of large sample size are non-existent and anecdotal cases are scattered throughout the literature. To obtain a clearer perspective of this emerging disease in children, we reviewed the medical literature for cases of Legionnaires' disease in children. To ensure the reported cases were indeed definitive cases of Legionnaires' disease, we excluded those reports in which only a single raised serology titre was the basis for diagnosis (table 1). 43% (33/76) of all the reported cases occurred in the USA, possibly indicating a higher index of suspicion of US physicians and availability of legionella diagnostic tests. No cases have been reported in developing countries, probably because diagnostic tests are less available in these countries.

	Paediatric patients
Age	
Mean, median	52, 24 months
Range	5 days to 228 months
Neonates (<2 months)*	13 (19%)
Infants (2–12 months)*	13 (19%)
Children (older than 12 months)*	42 (62%)
Sex	
Male†	41 (61%)
Female†	26 (39%)
Country	
USA	33 (43%)
Spain	10 (13%)
Italy	7 (9%)
Germany	5 (7%)
Canada	5 (7%)
France	4 (5%)
Japan	2 (3%)
Switzerland	2 (3%)
Austria	1 (1%)
England	1 (1%)
Finland	1 (1%)
Netherlands	1 (1%)
Israel	1 (1%)
Norway	1 (1%)
Portugal	1 (1%)

*Data on age only available for 68 patients. †Data on sex only available for 67 patients.

Table 3: **Demographic characteristics of 76 paediatric patients with Legionnaires' disease**

Underlying condition	Number (% of total cases)
Malignancy	
Leukaemia	10 (13%)
Astrocytoma	1 (1%)
Lymphoma	1 (1%)
Total	12 (16%)
Transplantation	
Kidney	5 (7%)
Liver	1 (1%)
Heart	1 (1%)
Bone marrow	2 (3%)
Total	9 (12%)
Congenital immunodeficiency	4 (5%)
Corticosteroid therapy	30 (39%)
Neonate (<2 months old)	13 (17%)
Any immunosuppressive condition*	50 (66%)
Underlying respiratory diseases	
Asthma	5 (7%)
Other respiratory diseases†	13 (11%)
Total	18 (24%)
Other conditions‡	5 (7%)
Any underlying conditions (immunosuppressed, respiratory disease, and other)	49 (78%)

*Any immunosuppressive condition including malignancy, transplantation, steroid use, congenital immunodeficiency and age <2 months. †Other respiratory diseases including aspiration, tracheobronchomalacia, pneumothorax, bronchopulmonary dysplasia, follicular bronchiolitis, hyaline membrane disease. ‡Other conditions including Downs syndrome (two cases), burns, congenital heart disease, biliary atresia.

Table 4: **Underlying conditions among paediatric patients with Legionnaires' disease**

Legionella infections were first reported in immunocompromised children with leukaemia, bone marrow transplantation, and chronic granulomatous disease patients.[10,17,45] Immunosuppression including malignancy, transplantation, corticosteroid use, and neonates with pre-existing lung conditions were risk factors for paediatric Legionnaires' disease (table 4). In adults, cigarette smoking, chronic lung diseases, alcohol, renal failure, advanced age, and immunosuppression were the primary risk factors. With the exception of cigarette smoking and renal failure, paediatric patients shared risk factors similar to those of adult patients—ie, presence of immunosuppression including corticosteroids and pre-existing lung disease. Extremes of ages were seen for both adult and paediatric groups—ie, neonates and advanced age are risk factors for Legionnaires' disease.

The symptoms and signs of paediatric Legionnaires' disease are non-specific; fever, cough, tachypnoea, and hypoxia were the most commonly encountered (table 5). Chest pain and haemoptysis were infrequently reported. Diarrhoea is often implicated as one of the extrapulmonary symptoms in adults with Legionnaires' disease, but it was reported in only ten paediatric patients (table 5). 17% (13/76) of the patients required mechanical ventilation, indicating intensive care unit admission, which is a frequent occurrence in adult Legionnaires' disease patients. Hyponatraemia is a frequent finding in adult patients yet it was seldom reported in paediatric cases. Overall, the laboratory results appeared to be non-specific and were not helpful in the diagnosis of Legionnaires' disease in paediatric patients. Pulmonary infiltrates on chest radiograph were documented in 97% of children with Legionnaires' disease. Pleural effusion was a common finding (table 6).

Hospital-acquired Legionnaires' disease

In 1989, an outbreak of paediatric Legionnaires' disease was first reported from Columbus, OH, USA.[10] Of the seven described patients, five received immunosuppressive therapy including corticosteroids. All patients presented with rapid onset of dyspnoea (less than 48 hours). All patients except one recovered after

Symptom	Number (%)
Fever*	48 (98%)
Respiratory†	
Cough	37
Tachypnoea	22
Dyspnoea	19
Wheezing	9
Rhinorrhoea	8
Chest pain	8
Cardiovascular†	
Tachycardia	10
Bradycardia	1
Hypotension	6
Neurological†	
Lethargy	8
Mental status changes	5
Headache	6
Seizure	1
Gastrointestinal†	
Diarrhoea	10
Abdominal pain	5
Anorexia	3
Vomiting	4
Hepatosplenomegaly	9
Rash†	3
Lymphadenopathy†	3
Mortality	25 (33%)

*Data available for 49 patients only. †Percentages not calculated because denominators were not available for all patients—ie, absence of symptoms was not explicitly mentioned.

Table 5: **Symptoms of paediatric patients with Legionnaires' disease**

Finding	Frequency, % (n/N)
Infiltrate	97 (61/63)
Unilateral	55 (31/56)
Bilateral	45 (25/56)
Effusion	30 (19/63)
Cavity	18 (11/63)
Nodules	8 (5/63)
Pneumothorax	6 (4/63)

Denominators vary because not all reports gave explicit descriptions of chest radiographs.

Table 6: **Chest radiographs of paediatric patients with Legionnaires' disease**

	Hospital acquired, % (n/N)	Community acquired, % (n/N)
Underlying conditions		
Any immunosuppression	90 (37/41)	37 (13/35)
Any respiratory disease	34 (14/41)	11 (4/35)
Any underlying condition	100 (41/41)	51 (18/35)
Age		
<12 months	50 (13/26)	50 (13/26)
≥12 months	59 (9/15)	40 (4/9)
Environmental link positive	88 (23/26)	33 (3/9)
Mortality	41 (17/41)	23 (8/35)

Patients were included only if all data was available including negative findings.

Table 7: **Comparison of paediatric patients with hospital-acquired and community-acquired *Legionella* spp infections**

appropriate treatment with erythromycin. 41 (54%) of the cases of paediatric Legionnaires' disease identified in this review were classified as hospital acquired. Compared with those with community-acquired Legionnaires' disease, patients with hospital-acquired Legionnaires' disease were more likely to be neonates, and to have underlying illnesses. The mortality was higher in hospital-acquired cases compared with community-acquired cases (41% *vs* 23%, respectively; table 7).

Environmental source and transmission

Based on numerous studies in adults, the source of hospital-acquired Legionnaires' disease is the hospital drinking water supply.[58] A positive environmental link was identified in 88% of hospitalised cases of paediatric Legionnaires' disease in whom environmental cultures were obtained (table 7). Tap water, hot water tanks, sinks, showerheads, respiratory therapy equipment, and humidifiers were the most commonly reported sites colonised with *Legionella* spp.

Community-acquired Legionnaires' disease

35 (46%) of the reported cases reviewed here were community acquired. Only 37% of patients with community-acquired Legionnaires' disease were immunosuppressed, by contrast with 90% of hospital-acquired cases. The first case report of paediatric community-acquired Legionnaires' disease was a 2·5-year-old boy with acute lymphocytic leukaemia.[45] The diagnosis of Legionnaires' disease was confirmed by fourfold rise of serology. The boy survived, although he did not receive antibiotics active against Legionnaires' disease. Environmental cultures were not done.

In 1997, one of us (RF) reported culture-confirmed cases of Legionnaires' disease in two neonates (9 days and 2 months old) who were not treated initially for legionella infection.[18] Both presented with fever and severe pneumonia with cavitary lesions on chest radiograph. The undiagnosed and untreated baby died. The second baby recovered after receiving erythromycin therapy.

No outbreak of paediatric Legionnaires' disease of community-acquired origin has been reported to our knowledge. The home water distribution system was documented to be the source in two children with community-acquired Legionnaires' disease. The legionella isolated from the tap water from home was identical to that obtained from the patient by pulse field gel electrophoresis.[48] In another epidemiological report, a previously healthy 4-year-old boy presented with severe pleural effusion and diaphragmatic paralysis; environmental cultures from his parents' and grandparents' house were negative for *L pneumophila*.[8]

Neonatal cases

Levy and Rubin reviewed nine cases of neonatal legionellosis reported in the literature;[60] the main findings were that all were hospital acquired, four were premature infants and five were term. Eight cases had potential risk factors including prematurity, bronchopulmonary dysplasia, and corticosteroid use. An environmental link to the hospital water distribution system was documented for four patients. An incubator and humidifier were implicated in one case.[61] Mortality was 55%. In our review, four additional neonatal cases

	Lived, % (n/N)	Died, % (n/N)
Age		
<12 months	27 (12/44)	58 (10/24)
Underlying diseases		
Immunosuppressed	57 (29/51)	84 (21/25)
Respiratory disease	18 (9/51)	32 (8/25)
Any comorbidity	71 (36/51)	92 (23/25)
Community acquired	53 (27/51)	32 (8/25)
Hospital acquired	47 (24/51)	68 (17/25)
Appropriate antibiotic	76 (29/34)	24 (9/21)
Inappropriate antibiotic	24 (5/34)	76 (12/21)

Appropriate antibiotic=antibiotic active in vitro against *Legionella* spp. Data not available for all patients so denominators do not total 76 for age and antibiotic administration.

Table 8: **Comparison of mortality in paediatric patients with Legionnaires' disease**

were identified, accounting for 13% of all reported cases of paediatric Legionnaires' disease. Three (23%) cases were community acquired. An environmental link was found for three hospital-acquired cases and one community-acquired case.[18,20,48] A hospital birthing pool was the source for Legionnaires' disease in a 7-day-old neonate who presented with fever, dyspnoea, and bilateral pneumonia. In this case, the urine antigen test was positive and legionella antibodies were raised (the mother's antibody tests were negative).[20]

Mortality

Overall, the mortality rate was 33%, and was notably higher in immunosuppressed patients and in children younger than 1 year of age (table 8). Of clinical relevance was that mortality was 23% in the 38 individuals who received appropriate antibiotics, and 70% in the 17 who received inappropriate antibiotics.

Search strategy and selection criteria

We searched Medline with the following keywords: "Legionella", "children", "infant", "neonates", "infection", and "Legionnaires' disease". All case reports and case series were reviewed to identify other reports of paediatric legionellosis. Inclusion criteria were based on diagnostic tests for Legionnaires' disease. A case was included if at least one of the following diagnostic methods was positive: culture of respiratory secretions, direct fluorescent antibody assay, urine antigen, or serology. If serology was the only diagnostic test positive, at least a fourfold increase in antibody titres was required for inclusion, so that cases based on only a single serological test were excluded. A structured case report form was completed for each case. Data collection included demographic and clinical information as well as epidemiological investigations into the source of the organism.

Future studies

The reported clinical characteristics of paediatric cases of Legionnaires' disease could be highly skewed, as in the original cases of Legionnaires' disease discovered in adults. The first observed cases tended to be in adults with severe pneumonia that was unresponsive to therapy. As rapid diagnostic tests became available, particularly the urinary antigen, it became easier to diagnose cases, and a larger group of patients was discovered. As investigators and clinicians began to screen for Legionnaires' disease systematically in observational studies of community-acquired pneumonia, a different picture emerged. Instead of a classic scenario of patients with severe pneumonia with a high mortality rate, patients were often found to have symptoms of pneumonia that resolved with earlier treatment.

Presuming that Legionnaires' disease is an under-diagnosed syndrome in children, how might this be established? Since it would not appear to be productive to investigate every child with pneumonia with a diagnostic test for legionella, we suggest one approach that might be cost effective. It would seem rational to apply legionella testing for patients who have contracted pneumonia in hospitals known to have a water supply colonised with *Legionella* spp, since the major risk factor is exposure to potable drinking water colonised with *Legionella* spp. It is no coincidence that paediatric outbreaks of hospital-acquired Legionnaires' disease were seen in paediatric hospitals at Ohio State University, University of Pittsburgh, and Stanford Hospitals, since outbreaks of hospital-acquired Legionnaires' disease had already occurred in adult patients at these hospitals.[10,23] Once the laboratory tests became available in these institutions, the affiliated paediatric hospitals had the diagnostic methodologies to uncover Legionnaires' disease. Even more importantly, disinfection measures directed at the hospital water distribution system can prevent the infection.

Case reports have generally focused on the novelty of occurrence of Legionnaires' disease in a paediatric patient. Although unusual clinical presentations, new underlying diseases, and infections by unusual *Legionella* species should still be reported, the message that an immunocompromised patient is susceptible to an opportunistic pathogen is becoming less novel. Of the reports in hospitals in which environmental cultures of the water distribution system were done, five explicitly discussed aspiration as a potential mode of transmission.[10,11,20,30,51] In one case of community-acquired Legionnaires' disease, aspiration was suspected as the mode of transmission. Thus, case studies should certainly include results of environmental cultures of drinking water since aspiration seems to be a major mode of transmission in paediatric legionellosis and potable water is the likely source.

Awareness of *Legionella* spp as a potential cause of paediatric pneumonia is particularly important because infection is unusually severe and life threatening. The antimicrobial therapy often used for empirical therapy in paediatric community-acquired pneumonia might not be efficacious against *Legionella* spp. In any case of pneumonia non-responsive to beta-lactam antibiotic therapy, Legionnaires' disease should be considered and specific diagnostic tests to verify this diagnosis should be done. As diagnostic modalities for legionella become more widely applied, we predict that legionellosis might appear as an emerging infectious disease in children.

Conflicts of interest

We declare that we have no conflicts of interest.

References

1 Muldoon RL, Jaecker DL, Kiefer HK. Legionnaires' disease in children. *Pediatrics* 1981; **67:** 329–32.

2 Mundel G, Goldberg A, Boldur I, Sompolinsky D, Katz Y. Legionnaires' disease in Israel: serological evidence of childhood infection. *Isr J Med Sci* 1983; **19:** 380–82.

3 Anderson RD, Laurer BA, Fraser DW, Hayes PS, McIntosh K. Infections with *Legionella pneumophila* in children. *J Infect Dis* 1981; **143:** 386–90.

4 Anderson R, Bergan T, Halvorsen K, Orstavik I. Legionnaires' disease combined with erytema multiforme in a 3-year-old boy. *Acta Pediatr Scand* 1981; **70:** 427–31.

5 Abernathy-Carver KJ, Fan LL, Boguniewicz M, Larsen GL, Leung DY. *Legionella* and *Pneumocystis* pneumonias in asthmatic children on high doses of systemic steroids. *Pediatr Pulmonol* 1994; **18:** 135–38.

6 Ahrens F, Hell W, Hollandt H, Lewald H, Paust H. Legionellosis in a newborn infant. *Monatsschr Kinderheilkd* 1993; **141:** 711–13 (in German).

7 Aubert G, Bornstein N, Rayet I, Pozzetto B, Lenormand P. Nosocomial infection with *Legionella pneumophila*, serogroup 1 and 8 in a neonate. *Scand J Infect Dis* 1990; **22:** 267–70.

8 Bettencourt JD, Barroso A, da Mota HC. Severe pleural effusion due to *Legionella pneumophila* respiratory infection. *Arch Pediatr Adolesc Med* 1994; **148:** 1218–19.

9 Beyer P, Kahn D, Horbach J, Schmid H, Graf W, Weber B. Unusual progression of a *Legionella pneumopila* infection in a young child. *Eur J Pediatr* 1984; **141:** 173–75.

10 Brady M. Nosocomial Legionnaires' disease in a children's hospital. *J Pediatr* 1989; **115:** 46–50.

11 Campins M, Ferrer A, Callis L, et al. Nosocomial Legionnaires' disease in a children's hospital. *J Pediatr Infect Dis* 2000; **19:** 228–34.

12 Carlson NC, Kuskie MR, Dobyns EL, Wheeler MD, Roe MH, Abzug MJ. Legionellosis in children: an expanding spectrum. *Pediatr Infect Dis J* 1990; **9:** 133–37.

13 Aebischer CC, Matter L, Gaia V, Aebi C. Diagnosis by polymerase chain reaction of pneumonia caused by *Legionella pneumophila* in a immunocompetent child. *Infection* 1999; **27:** 280–82.

14 Castellani Pastoris M, Nigro G, Midulla M. Arrhythmia or myocarditis: a novel clinical form of *Legionella pneumophila* infection in children without pneumonia. *Eur J Pediatr* 1985; **144:** 157–59.

15 Couvreur J, Dournon E, Garcia J, Sardet-Frismand A, Just J, Tournier G. Legionnaires' disease in children. Epidemiological survey with a new case report and review of the literature. *Ann Pediatr* 1986; **33:** 379–84.

16 Cutz E, Thorner PS, Rao T, Toma S, Gold R, Gelfand EW. Disseminated *Legionella pneumophila* infection in an infant with severe combined immunodeficiency. *J Pediatr* 1982; **199:** 760–62.

17 Ephros M, Engelhard D, Maayan S, Bercovier H. *Legionella gormanii* pneumonia in a child with chronic granulomatous disease. *Pediatr Infect Dis J* 1989; **8:** 726–27.

18 Famiglietti RF, Bakerman PR, Saubolle MA, Rudinsky M. Cavitary legionellosis in two immunocompetent infants. *Pediatrics* 1997; **99:** 899–903.

19 Ferrer A, Elcuaz RI, Giménez-Pérez M, Iglesias J, Fernádez-Pérez F. Childhood legionellosis. *Enferm Infecc Microbiol Clin* 1990; **8:** 278–81 (in Spanish).

20 Franzin L, Scolfara C, Cabodi D, Valera M, Tove PA. *Legionella pneumophila* pneumonia in a newborn after water birth: a new mode of transmission. *Clin Infect Dis* 2001; **33:** 103–04.

21 Fuchs GJ III, LaRocco M, Robinson A, Kohl S. Fatal Legionnaires' disease in an infant. *Pediatr Infect Dis J* 1986; **5:** 377–79.

22 Gervaix A, Beghetti M, Rimensberger P, Posfay-Barbe K, Barazzone C. Bullous emphysema after *Legionella* pneumonia in a two-year-old child. *Pediatr Infect Dis J* 2000; **19:** 86–87.

23 Green M, Wald ER, Dashefsky B, Barbadora K, Wadowsky RM. Field inversion gel electrophoretic analysis of *Legionella pneumophila* strains associated with nosocomial legionellosis in children. *J Clin Microbiol* 1996; **34:** 175–76.

24 Greene KA, Rhine WD, Starnes VA, Ariagno RL. Fatal postoperative *Legionella pneumonia* in a newborn. *J Perinat* 1990; **10:** 183–84.

25 Gutzeit M, Laver S, Dunne WM, Kelly K, Chusid M. Fatal legionella pneumonitis in a neutropenic leukemic child. *Pediatr Infect Dis J* 1987; **6:** 68–69.

26 Hartemann E, Berthier JC, Barrois S, et al. Severe legionella pneumopathy in an immunologically normal infant. *Pediatrie* 1983; **38:** 393–99 (in French).

27 Hervas J, Lopez P, de la Fuente A, Alomar P. Multiple organ system failure in an infant with Legionella infection. *Pediatr Infect Dis J* 1988; **7:** 671–73.

28 Holmberg RE, Pavia AT, Montgomery D, Clark JM, Eggert LD. Nosocomial *Legionella* pneumonia in the neonate. *Pediatrics* 1993; **92:** 450–53.

29 Horie H, Kawakami H, Minoshima K, et al. Neonatal Legionnaires' disease. Histopathological findings in an autopsied neonate. *Acta Pathol Japan* 1992; **42:** 427–31.

30 Joly JR, Dery P, Gauvrau L, et al. Legionnaires' disease caused by *Legionella dumoffi* in distilled water. *CMAJ* 1986; **135:** 1274–77.

31 Kovatch AL, Jardine DS, Dowling JN, Yee RB, Pasculle AW. Legionellosis in children with leukemia in relapse. *Pediatrics* 1984; **73:** 811–15.

32 Krugmann J, Sailer-Höck M, Muller T, Gruber J, Allerberger F, Offner FA. Epstein-Barr virus-asociated Hodgkin's lymphoma and *Legionella pneumophila* infection complicating treatment of juvenile rheumatoid arthritis with methotrexate and cyclosporine A. *Hum Pathol* 2000; **31:** 253–55.

33 Kugler JW, Armitage JO, Helms CM, et al. Nosocomial Legionnaires' disease: occurrence in recipients of bone marrow transplants. *Am J Med* 1983; **74:** 281–88.

34 Kulhanjian J, Schecter R. Fatal pneumonia in a seven-month-old infant. *Pediatr Infect Dis J* 1994; **13:** 334–35.

35 La Scola B, Michel G, Raoult D. Isolation of *Legionella pneumophila* by centrifugation of shell vial cell cultures from multiple liver and lung abscesses. *J Clin Microbiol* 1999; **37:** 785–87.

36 Levy DA, Bens MS, Craun GF, Calderon RL, Herwaldt BA. Surveillance for waterborne disease outbreaks – United States 1995–1996. *MMWR CDC Surveill Summ* 1998; **7:** 1–33.

37 Masuda T, Ishikawwa Y, Akasaka Y, et al. Follicular bronchiolitis (FBB) associated with *Legionella pneumophila* infection. *Pediatr Pathol Mol Med* 2002; **21:** 517–24.

38 Millunchick EW, Floyd J, Blanks J. Legionnaires' disease in an immunologically normal child. *Am J Dis Child* 1981; **135:** 1065–66.

39 Negre V, Chevallier B, Dournon E, et al. Nosocomial Legionnaires' disease in children. Preventive measures. *Arch Fr Pediatr* 1990; **47:** 43–45 (in French).

40 Nigro G, Castellani Pastoris M, Mazzotti FM, Midulla M. Acute cerebellar ataxis in pediatric legionellosis. *Pediatrics* 1983; **72:** 847–48.

41 Peerless AG, Liebhaber M, Anderson S, et al. Legionella pneumonia in chronic granulomatous disease. *J Pediatr* 1985; **106:** 783–85.

42 Peliowski A, Finer NN. Intractable seizures in Legionnaires' disease. *J Pediatr* 1986; **109:** 657–58.

43 Qin X, Abe PM, Weissman SJ, Manning SC. Extrapulmonary *Legionella micdadei* infection in a previously healthy child. *Pediatr Infect Dis J* 2002; **21:** 1174–76.

44 Quaresima T, Castellani Pastoris M. Infezioni da *Legionella* sp. nel bambino. *Riv Ital Pediatr* 1992; **18:** 125–36.

45 Ryan ME, Feldman S, Pruitt B, Fraser DW. Legionnaires' disease in a child with cancer. *Pediatrics* 1979; **64:** 951–53.

46 Simpson RM, Gogswell JJ, Mitchell ER, Macrae AD. Legionnaires' disease in an infant. *Lancet* 1980; **2:** 740–41.

47 Sturm R, Staneck JL, Myers JP, Wilkinson HW, Cottrill CM, Towbin RB. Pediatric Legionnaires' disease: diagnosis by direct immunofluorescent staining of sputum. *Pediatrics* 1981; **68:** 539–43.

48 Skogberg K, Nuorti P, Saxen H, et al. A newborn with domestically acquired Legionnaires' diseaze confirmed by molecular typing. *Clin Infect Dis* 2002; **35:** e82–85.

49 Tokunaga Y, Concepcion W, Berquist D, et al. Graft involvement by legionella in a liver transplant recipient. *Arch Surg* 1992; **127:** 457–77.

50 Trubel HK, Meyer HG, Jahn B, Knuf M, Kamin W, Huth R. Complicated nosocomial pneumonia due to *Legionella pneumophila* in an immunocompromised child. *Scand J Infect Dis* 2002; **34:** 219–21.

51 Visca P, Goldoni P, Luck PC, et al. Multple types of *Legionella pneumophila* serogroup 6 in a hospital heated-water system associated with sporadic infections. *J Clin Microbiol* 1999; **37:** 2189–96.

52 Womack S, Liang KC, Llagan N, Weyhing BG, Planas A. *Legionella pneumophila* in a preterm infant—a case report. *J Perinatol* 1992; **12:** 303–05.

53 Quagliano PV, Das Narla L. Legionella pneumonia causing multiple cavitating pulmonary nodules in a 7-month-old infant. *Am J Roentgenol* 1993; **161:** 367–68.

54 Orenstein WA, Overturf GD, Leedom JM, et al. The frequency of legionella infection prospectively determined in children hospitalized with pneumonia. *J Pediatr* 1981; **99:** 403–06.

55 Orme RL, Haas L, Craickshank JG, et al. Legionnaires' disease in infants. *Lancet* 1980; **2:** 1027.

56 Peeters M, Cornu G, De Meyer R. Legionnaires' disease in an immunosuppressed child. *Acta Pediatr Belg* 1980; **33:** 189–93.

57 Stout JE, Yu VL. Current concepts: legionellosis. *N Engl J Med* 1997; **337:** 682–87.

58 Sabria M, Yu VL. Hospital-acquired legionellosis: solutions for a preventable disease. *Lancet Infect Dis* 2002; **2:** 368–73.

59 Benin AL, Benson RF, Besser RE. Trends in Legionnaires' disease, 1980–1998: declining mortality and new patterns of diagnosis. *Clin Infect Dis* 2002; **35:** 1039–46.

60 Levy I, Rubin LG. Legionella pneumonia in neonates: a literature review. *J Perinatol* 1998; **18:** 287–90.

61 Luck PD, Reichelt G, Witzieb W, Muschner K. Legionella pneumonia in a 3-year-old child. *Kinderarztl Praxis* 1987; **55:** 431–36.