



REPORTED MORBIDITY
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MONTHLY MORBIDITY REPORT

Provisional Statistics

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OFFICE OF PUBLIC HEALTH STATISTICS

DEPARTMENT OF HEALTH
AND HUMAN RESOURCES
OFFICE OF HEALTH SERVICES
AND ENVIRONMENTAL QUALITY

Legionnaires' Disease: Preliminary Report Its Diagnosis, Etiology, Pathology, And Therapy

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Although there is still much to be learned, enough information has been gathered about the Legionnaires' disease and its etiologic agent that a preliminary composite of the salient features of the disease, its course, and approach to the diagnosis and therapy can be formulated. Evidence strongly suggests that the same bacterium which caused the outbreak of pneumonia in Philadelphia in 1976 also caused outbreaks in the District of Columbia in 1965, in Pontiac, Michigan in 1968, and in Philadelphia in 1974. Since August 1976, over 20 sporadic cases of pneumonia associated with the same bacterium have been identified from 11 States. Of these sporadic cases, the diagnosis in two was first made by isolating the organism on bacteriologic medium; in a third case, the isolation of the agent was made by inoculating postmortem lung tissue into a guinea pig; the remaining cases were diagnosed by demonstrating significant rises in titer in paired sera. Clearly, the disease is neither localized nor new.

CLINICAL FINDINGS:

Legionnaires' disease begins 2 to 10 days after exposure. In the typical case, the earliest symptoms are malaise, muscle aches, and a slight headache. Within less than a day, there is a rapidly rising fever associated with chills. A nonproductive cough is common early, often with the onset of initial symptoms. Abdominal pain and gastrointestinal symptoms also occur in many of the patients. Temperatures commonly reach 102 to 105 F (39-41 C). When first examined by a physician, most patients have been found to have rales without evidence of consolidation.

The rest of the findings on physical examination are usually normal, although some patients have been obtunded. Initial laboratory findings often include a leukocytosis (in 60%) with a left shift, 3+ proteinuria or greater (in 20%), erythrocyte sedimentation rate greater than 80 mm per hour (in 33%), and, in a significant minority, hyponatremia, mild azotemia, and elevation of the serum glutamic oxaloacetic transaminase (SGOT) and alkaline phosphatase. Chest x-rays show patchy, interstitial infiltrates or areas of consolidation which progress to more widespread consolidation. Effusions, when present, are usually minimal.

Illness usually progresses over the 2 to 3 days after hospitalization. Cough commonly becomes productive, but the sputum is rarely purulent. Approximately 15% of the patients die, either of shock or respiratory failure. Upper and lower gastrointestinal bleeding is not uncommon, but may be related to the stress of illness. Renal failure has been seen in several patients. In those who recover, the radiographic evidence of improvement lags a few days behind clinical resolution.

CHEMOTHERAPY:

No randomized trial of antibiotic therapy has been performed. Of the drugs used, cephalothin has been associated with a relatively high case-fatality ratio and erythromycin and tetracycline, with relatively low case-fatality ratios. These associations with case-fatality ratios, however, may be as much a reflection of the physician's assessment of the severity of illness as they are indications of the efficacy of drug treatment. Agar dilution susceptibility testing has shown the organism to be "susceptible" or "moderately susceptible" to a large number and a wide variety of antibiotics. In general, erythromycin, a number of penicillins, cephal-

SOURCE:

CDC Special Communication, September, 1977.

osporins, aminoglycosides, chloramphenicol, rifampin, and sulfamethoxazole-trimethoprim produce *in vitro* results in the "susceptible range"; tetracycline and methicillin minimum inhibitory concentrations (MIC) were borderline, and vancomycin MIC suggested resistance. There *in vitro* interpretations do not always correlate with *in vivo* response. Tests in embryonated eggs showed rifampin, gentamicin, streptomycin, and erythromycin to be most effective in that order. Erythromycin has been effective against experimental infection in guinea pigs. Similar studies with other antibiotics are under way. At present, it is impossible to say what is the best antibiotic to use in treating patients with Legionnaires' disease, but erythromycin appears to be a promising agent.

PATHOLOGY:

In fatal human cases, the pneumonia caused by the Legionnaires' disease organism has been of the lobar type. Since we have not had the opportunity to examine lung biopsy tissues from patients surviving the disease, we cannot characterize early lesions or milder manifestations of the disease. In paraffin sections the organism stains poorly with tissue gram stains (i.e. Brown-Brenn and Brown-Hopps stains) and the giemsa stain. It does not stain at all with hematoxylin and eosin, acid fast, Gimenez, and methenamine silver stains. In our experience the Dieterle silver impregnation procedure consistently demonstrates the organism in paraffin-embedded sections. The largest number of organisms is associated with intraalveolar proteinaceous debris and infiltrates of polymorphonuclear neutrophils and macrophages.

ISOLATION AND IDENTIFICATION OF THE ETIOLOGIC AGENT:

The initial isolations of the bacterium of Legionnaires' disease were made in guinea pigs inoculated with lung tissues obtained postmortem from 4 patients. The guinea pigs developed a febrile illness characterized by watery eyes and prostration 1 to 2 days after inoculation. Moribund animals were sacrificed 3 to 6 days after onset of fever, and specimens from the spleen, liver, and lungs were inoculated into 7-day-old embryonated hens' eggs. The eggs died 4 to 6 days after inoculation, and smears of yolk sacs stained by the Gimenez method showed bacilli 0.3-0.4 μ m in width and of various lengths. The etiologic role of the bacterium was established by indirect fluorescent antibody (IFA)

tests with appropriate sera from patients with Legionnaires' disease.

Primary isolation on bacteriologic media of the bacterium considered to be the etiologic agent has been obtained in five reported instances. In three cases--two Legionnaires' cases and one sporadic case this year--lung tissue obtained postmortem was successfully cultured on an agar medium. In two cases, the organism was isolated from pleural fluid obtained before the patients' death, both of whom were taking corticosteroids for an underlying autoimmune disease. There is no reported experience with attempts to isolate the organism from sputum. However, should sputum, transtracheal aspirations, bronchial washings, or endotracheal aspirations be submitted to the laboratory with the request that isolation of the Legionnaires' organism be attempted, the microbiologist should use Mueller-Hinton or GC agar (or their equivalents) containing 1% hemoglobin and 2% enrichment (Isovitalex* - BBL - or its equivalent). Although hemoglobin is preferred, 5% Fildes enrichment (peptic digest of sheep blood) can be substituted for hemoglobin. Growth will also occur in Mueller-Hinton broth supplemented with Fildes enrichment (3%-4%) and Isovitalex (2%). The final pH of these media should be adjusted to pH 6.9 to 7.0.

Although the organism can grow when incubated at 35C in air, better growth is obtained with incubation in a candle extinction jar or in 5% CO₂. The time of incubation required before growth can be detected macroscopically appears to be related to the size of the inoculum. To provide as large an inoculum as possible, one area of an agar plate should be inoculated with the clinical material, such as pleural fluid or lung tissue, and not streaked. Another area of the plate or a second plate should be inoculated and streaked for isolation. Incubate plates for 5 to 10 days before discarding as negative.

Gram stain shows the organisms as gram negative rods, approximately 0.5 x 0.7 μ m wide, and 2 to 3 μ m in length. The length however, is variable and rods up to 20 μ m or longer have been observed. These longer forms are frequently curved. Cells are frequently vacuolated on primary isolation and early passage on agar. Vacuolated areas stain with sudan black B. Various characteristics of the organism are summarized below:

Mueller-Hinton agar with hemoglobin & Isovitalex	Growth
Mueller-Hinton agar	No growth
Mueller-Hinton agar with X & V factors	No growth
Blood agar	No growth
Oxidase	Weakly positive by Kovacs method; (tetramethyl P-phenylenediamine dihydrochloride reagent)
Catalase	Positive, 72 H cultures
Growth, 3 days at: 42 C 35 C 25 C	Negative Positive Negative
Pigment	Soluble brown pigment produced; best demonstrated on medium with Fildes enrichment; observable first in area of confluent growth
Urea	No reaction when Christensen urea slant is inoculated heavily; probably does not grow on medium
Gelatin	Positive, 48 H (API* 20E gelatin inoculated with turbid suspension of organisms in distilled water)

*Use of trade names is for identification only and does not constitute endorsement by the Public Health Service or by the U.S. Department of Health Education, and Welfare.

The Legionnaires' disease organism grows slowly. However, after 3 or 4 passages on agar it will produce a heavy growth within 3 days in areas where the inoculum is sufficient to produce confluent growth. Individual colonies are very small at 48-72 H. In 4-5 days, some colonies will be 1-2 mm or larger in diameter. On initial isolation of the organism from previously inoculated yolk sac membranes, two populations of colonies were observed. One type of colony was punctate at 3 days and did not enlarge. The second colony type continued to enlarge, reaching a diameter of 1-2 mm or larger. Whether these two colony types are a constant feature of the organism is not yet known.

We have also conducted gas liquid chromatography (GLC) studies with a number of Legionnaires' disease isolates to assess their chemical relatedness. GLC analysis of cellular fatty acids showed that each isolate possessed essentially the same fatty acids, which were characterized by large amounts of branch-

ed-chain acids. The presence and relative concentration of these branched fatty acids and the absence of other acids generally present in other gram-negative bacteria constitute a unique fatty acid profile for these isolates. These and other findings will ultimately be useful in the classification of this organism.

SEROLOGIC DIAGNOSIS:

The IFA test, with suspected patients' acute and convalescent paired sera and a freshly thawed yolk sac suspension of the Legionnaires' organism as antigen, currently remains the test of choice. Other tests, including microagglutination and complement fixation, are being evaluated, but none has achieved the level of sensitivity or specificity of the IFA test.

At this time, the serologic procedures appear to be the most important laboratory tools for the diagnosis of Legionnaires' disease. Efforts are underway to develop a sensitive, yet practical, serologic test which could be made readily available to all serology laboratories. Until such a test is available, serum specimens should be submitted to:

Central Laboratory
La. Department of Health and Human Resources
325 Loyola Avenue, 7th Floor
New Orleans, Louisiana 70112

As usual, specimens must be accompanied with a summary of the patient's clinical history, including dates of onset and dates specimens were taken. Sample of acute and convalescent sera should be submitted. Diagnostic titers may appear in sera obtained as early as the second week of illness, but the greatest proportion of diagnostic titers has occurred in sera obtained 22 to 60 days after the onset of illness. Thus, the acute serum specimen should be obtained as early as possible, and the convalescent specimens should include one taken after the third week. Specimens should be clearly marked as acute or convalescent.

Clinicians or laboratories requiring assistance should contact the Epidemiology Unit (504 568-5005) for preliminary consultation and support. The Center for Disease Control will provide additional consultation and support if needed.

SELECTED REPORTABLE DISEASES

(By Place of Residence)

STATE AND PARISH TOTALS	ASEPTIC MENINGITIS	DIPH THERIA	ENCEPHALITIS	ENCEPHALITIS, POST INFECTIOUS	HEPATITIS A AND UNSPECIFIED	HEPATITIS B	TUBERCULOSIS, PULMONARY	MENINGOCOCCAL INFECTIONS	PERTUSSIS	RABIES IN ANIMALS	RUBELLA*	SEVERE UNDERNUTRITION	SHIGELLOSIS	TYPHOID FEVER	OTHER SALMONELLOSIS	TETANUS	MEASLES	GONORRHEA	SYPHILIS, PRIMARY AND SECONDARY
Reported Morbidity October, 1977																			
TOTAL TO DATE 1976	57	0	26	4	430	144	426	37	14	8	90	8	75	3	102	2	221	16158	498
TOTAL TO DATE 1977	20	0	13	0	537	132	468	129	8	22	27	4	119	1	127	2	75	15927	596
TOTAL THIS MONTH	5	0	5	0	62	16	34	5	2	1	0	0	16	0	24	1	1	1811	56
ACADIA																		13	1
ALLEN																		2	
ASCENSION					3													7	
ASSUMPTION			1															3	
AVOUELLES																		2	
BEAUREGARD																		5	
BIENVILLE																		3	
BOSSIER	1												1		2			20	1
CADDO					4	1	4						2		3			146	2
CALCASIEU			1		3	3	1											82	
CALDWELL																			
CAMERON													2						
CATAHOULA							1											1	
CLAIBORNE																		16	
CONCORDIA																		5	
DESOTO							1											5	
EAST BATON ROUGE					4	1		1					1		1			205	12
EAST CARROLL																		2	
EAST FELICIANA							1												
EVANGELINE															1			1	
FRANKLIN																		10	
GRANT																		4	
IBERIA						1												15	1
IBERVILLE								1										12	
JACKSON																			
JEFFERSON	2		2		11	1	3	2							1			73	6
JEFFERSON DAVIS																		16	
LAFAYETTE																		23	2
LAFOURCHE									2									13	1
LASALLE																		1	
LINCOLN																		18	
LIVINGSTON																		4	
MADISON																		3	
MOREHOUSE																1		13	
NATCHITOCHE							2											20	
ORLEANS	2		1		20	4	6						7		6		1	691	20
OUACHITA					1		3											43	
PLAQUEMINES					4													6	
POINTE COUPEE																			
RAPIDES					2	1							1					66	3
RED RIVER																		1	
RICHLAND							2											7	
SABINE						1												4	
ST. BERNARD					1	1	1											7	
ST. CHARLES																		8	1
ST. HELENA																		6	
ST. JAMES							1											3	
ST. JOHN						1												6	
ST. LANDRY					3		1											7	2
ST. MARTIN																		3	
ST. MARY					1										1			3	
ST. TAMMANY													1		1			22	1
TANGIPAHOA							2											25	1
TENSAS																		1	
TERREBONNE					3	1		1										9	1
UNION																		7	
VERMILION					1													6	
VERNON																			
WASHINGTON					1		4								3			55	
WEBSTER							1			1			1					10	
WEST BATON ROUGE																		16	
WEST CARROLL																		19	
WEST FELICIANA																		8	
WINN																		26	1
OUT OF STATE																		1	
																		2	

* Includes Rubella, Congenital Syndrome

From January 1 through October 31, 1977, the following cases were also reported: 1-Brucellosis; 4-Leptospirosis; 2-Malaria (contracted outside the U.S.A.); 7-Rocky Mountain Spotted Fever.