Listeriosis in HIV-infected and AIDS Patients in San Francisco, Alameda and Contra Costa County

by

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B.A. (University of California at Santa Cruz) 1987

THESIS

Submitted in partial satisfaction of the requirements for the degree of Masters Science in Health and Medical Sciences in the GRADUATE DIVISION of the UNIVERSITY of CALIFORNIA at BERKELEY

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University of California at Berkeley

1993
Listeriosis in HIV-infected and AIDS Patients in San Francisco, Alameda, and Contra Costa County

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Dedication

For their love, support, and encouragement, and for putting up with my griping, I dedicate this work to Ted and my mother, Sue.
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Acknowledgements

I am grateful and indebted to my thesis advisors Arthur Reingold, MD and John Swartzberg, MD for their guidance, assistance, insights, and help with this thesis since its inception. I also want to thank my thesis committee member Warren Winkelstein, MD for reading my thesis and giving advice. Gretchen Anderson, MPH, Pam Daily, MPH, and Kevin Krause at the Bacterial and Mycotic Surveillance Program gave me assistance and cheerful encouragement in collecting the data for this project. Charlotte Kent, PhD contributed the control data and was extremely helpful arranging and explaining the data discs. Thanks to the staff of the Joint Medical Program for providing the constant support and assistance that helped each day go by smoothly. Thanks to Vicky for being a great friend and for riding the weekly roller-coaster with me for the last three years. And, many thanks to my family members across the country whose constant presence (if only by mail or phone) continues to remind me of who I am and where I'm going.
CHAPTER ONE: LISTERIOSIS - INTRODUCTION and BACKGROUND

Listeria monocytogenes is a food-borne, bacterial pathogen that primarily infects immunocompromised individuals. It has caused several major epidemics in the United States in the last decade, and may well be the leading fatal foodborne infection in this country.

Historical

In the early 1900's researchers and clinicians had isolated organisms that were, in retrospect, probably Listeria monocytogenes. French clinicians isolated a "diphtheroid" from the spinal fluid of a patient with meningitis in 1919 (1). In 1924, an epizootic took place among laboratory rabbits in England. The organism was isolated and named Bacterium monocytogenes for the peripheral monocytosis it caused (2). This same organism apparently caused a second epizootic among rabbits along the Tiger River in South Africa. This disease was also characterized by monocytosis. The etiologic organism, originally coined the Tiger River Bacillus, was later renamed Listerella hepatolytica (1). (It is debated whether the organism was named in honor of Joseph Lister, the founder of aseptic technique, or whether it was named for the director of the South African Institute for Medical Research at Johannesburg at the time of the epizootic, Sir Spencer Lister (3)). The organism is now called Listeria
*monocytogenes*, again because of the monocytosis it causes in laboratory animals.

**Microbiology**

There are seven recognized species of *Listeria*, only one of which causes significant disease in humans and animals. *L. monocytogenes* is a Gram-positive, non-spore forming, facultative anaerobic rod. It is resistant to high concentrations of salt and alkali; high levels of desiccation; and can grow well in both hot and cold environments (4 C to 45 C) (2,4). The ability of *L. monocytogenes* to grow at cold temperatures is useful for laboratory studies. Cold enrichment techniques are used to isolate *L. monocytogenes* from non-sterile environments that include mixed bacterial flora (e.g. fecal specimens or food samples). Temperatures around 4 C permit the growth of *Listeria* while inhibiting the growth of other, competing bacteria (1,2). When grown at 20-25 C, *L. monocytogenes* demonstrates a characteristic "tumbling" motility (4).

Eleven serotypes of *L. monocytogenes* have been distinguished based on variations in the H and O surface antigens. However, 90% of disease in humans is caused by 3 serotypes, 1/2a, 1/2b, and 4b (3).

*Listeria* has an affinity for the phagocytic cells of the host and is capable of living and multiplying within the cytoplasm of host macrophages. *L. monocytogenes* produces a
hemolysin, called listeriolyisin O, which has been shown in vitro to destroy the cell membranes of macrophages (5). It has been hypothesized that, after L. monocytogenes has been phagocytosed by the host macrophage, listeriolyisin O lyses the phagocytic vacuoles and thus allows the organism to escape into the cytoplasm (4). Several other toxins are produced by L. monocytogenes, including a pyrogenic toxin, a hemorrhagic toxin, and a monocytopsis producing factor. However, these factors have not been well-correlated with virulence in laboratory studies (1).

Environmental

L. monocytogenes is ubiquitous in nature and can be cultured from soil, water, dust, sewage, animal feed and vegetable matter (4,6). Listeria has been isolated from over 50 species of animals, including domestic cattle, sheep, and fowl (1,6). It also has been isolated from fish, crustaceans, ticks, and fleas (1).

Disease due to L. monocytogenes was observed in veterinary medicine long before it was recognized in humans. Listeria can cause both septic abortion and a form of purulent basilar meningoencephalitis termed "circling disease" in sheep and cattle (4). Milk taken from diseased cows has been shown to contain high titers of L. monocytogenes (4,6). It is thought that disease in domestic
animals occurs when contaminated seed and silage is ingested (6).

Food Industry

Given how widely distributed L. monocytogenes is in soil, vegetable matter, and animals, it is not surprising that it has been cultured from many types of food eaten by people. The ability of L. monocytogenes to survive across a broad temperature range and its relative resistance to destruction by heating, freezing, salting, and chemicals, also contribute to the frequency with which it is found in foods (4).

Testing of meat and dairy products has determined the prevalence of Listeria in these foods. As many as 5% of raw milk products contain detectable L. monocytogenes (7). Of all cheeses, soft cheeses (Mexican style and Brie cheeses) are more likely to contain L. monocytogenes, with one study demonstrating 5-10% of samples contaminated (7). It is thought that the relatively high pH of these cheeses is particularly conducive to growth of L. monocytogenes (7, 8). Dairy products with a low pH, like cottage cheese and yougurt, on the other hand, do not support growth of L. monocytogenes and are rarely found to contain it. While many of the dairy products from which Listeria has been cultured are made from unpasteurized milk, L. monocytogenes has also been isolated from apparently adequately
pasteurized dairy products (20). Originally it was hypothesized that intracellular *L. monocytogenes* might be somewhat protected from the pasteurization process. However, numerous studies have indicated that pasteurization techniques, when properly performed, adequately kill *L. monocytogenes* (7). While survival of occasional organisms was found when milk with very high titers of intracellular *L. monocytogenes* was tested, such high titers would be expected to occur only in the milk of a very sick animal (7). The current hypothesis is that the presence of *Listeria* in products made from milk pasteurized according to regulations is due to post-pasteurization contamination.

*L. monocytogenes* has been recovered from 15 to 20% of raw beef products and up to 80% of samples of raw poultry (7). In addition, 4 to 8% of cooked crab, crustacean or shrimp samples contain *L. monocytogenes* (1,7). *L. monocytogenes* contamination of hot dogs (9), deli meats (10), pate, and vegetable products, especially pre-sliced and pre-packaged salads, has also been documented (7).

**Epidemiology**

Most invasive infections with *L. monocytogenes* (listeriosis) occur in persons with some level of depressed T-cell immunity: individuals at the highest risk for listeriosis include those with a malignancy (especially hematologic malignancy); those taking immunosuppressive
medication (corticosteroids or chemotherapy); patients with HIV/AIDS; the elderly and neonates (4,11,12,13). While *L. monocytogenes* has been detected in specimens obtained from the cervix, placenta, and amniotic fluid of pregnant women, it is the fetus, not the pregnant woman, who is at substantial risk of invasive disease. However, as many as 30% of invasive infections due to *L. monocytogenes* occur in apparently healthy adults (4,13,14). Meningitis and sepsis are the most common manifestations of invasive *L. monocytogenes* infection, while pneumonia, endocarditis, and peritonitis occur rarely.

Listeriosis is associated with a high mortality rate, even in those without an underlying immunosuppressive condition. Of the estimated 1700 cases of listeriosis occurring annually in the U.S, approximately 600 (35%) result in death (450 adult deaths and 150 fetal and neonatal deaths) (4).

*L. monocytogenes* is not infrequently a part of the normal intestinal and vaginal flora of humans, producing no disease. Studies have demonstrated that an estimated 1-5% of the population have vaginal or gastrointestinal colonization with *Listeria* without any clinical signs of disease (1,4). *L. monocytogenes* has been isolated in 4.5% of healthy slaughterhouse workers and as many as 26% of household contacts of listeriosis patients (4).
A number of studies have reported a seasonal pattern in the incidence of listeriosis, with more disease occurring in the late summer and early fall months (15). However, there is not agreement on this finding, as many studies have shown no seasonality of listeriosis (1).

A. Incidence

A recent Centers for Disease Control (CDC) national surveillance study has determined the baseline incidence rates of listeriosis in the U.S. The overall annual incidence rate was 7.1 cases per 1,000,000 population. The incidence of perinatal infections was 12.4 cases per 100,000 live births, while the rate of non-perinatal cases was 5.4 per 1,000,000 adults (1). The rates were highest at the extremes of age. Annual incidence rates of listeriosis in the early 1970’s and early 1980’s had been estimated at 0.5 and 3.6 per 1,000,000 population, respectively (3,16). From these numbers it would appear that the incidence of listeriosis has been increasing over the last 2 decades. It is possible that the incidence of listeriosis has increased because the number of immunocompromised patients at risk for listeriosis has increased. However, because listeriosis was not reportable in most states until the mid-1980s, and previous estimates were based on passive surveillance and retrospective data, it is highly likely that the earlier rates were substantially underestimated (16). Thus, it is
difficult to determine with certainty whether or not there has been a true increase in the incidence of listeriosis.

In general, incidence rates reported in Europe, the U.K. and in Canada are lower than those reported in the U.S. However, it is likely that these lower rates also reflect differences in reporting or surveillance, and they may not reflect a true difference in the occurrence of disease (1,17).

B. Case Fatality Ratios

According to the 1986 CDC study, the overall case-fatality ratio for non-perinatal cases was 35%, with the lowest ratios in those under 40 years of age (11%) and much higher ratios in those over 60 years of age (63%) (1). Another study indicated that, not surprisingly, outcome depended on the underlying condition of the patient. Sixty percent of cancer patients who contracted listeriosis died, while patients taking corticosteroids and alcoholics had lower fatality ratios (3).

C. Foodborne Transmission

Some of the first cases of listeriosis in humans occurred in veterinarians, ranchers, and poultry workers, who developed cutaneous lesions after handling infected animals (4). Thus, it was originally thought that listeriosis was a zoonosis, requiring direct contact with
infected animals. In subsequent years it was demonstrated that, in fact, most human cases of listeriosis occurred in urban settings in persons with no known animal exposures (1,4). It was hypothesized that a likely route of infection in these cases was consumption of contaminated foods.

The first investigation that conclusively demonstrated food-borne transmission of listeriosis was conducted in 1981 in Nova Scotia, Canada. An outbreak of *L. monocytogenes* serotype 4B infections occurred, including 34 perinatal cases and 7 non-pregnancy-associated cases. A case-control study was conducted to determine if animal, occupational or food exposures were associated with listeriosis. It was found that listeriosis was strongly associated with ingestion of coleslaw in the three months preceding illness. The source of the epidemic was then traced to coleslaw made from cabbage grown at a local farm. The farmer had used sheep manure to fertilize his crops and had had 2 sheep die of *L. monocytogenes* infection during the period of the outbreak (18). Also in 1981, an outbreak of 22 perinatal cases of listeriosis, serotype 1b, was suspected to be linked with consumption of shellfish (19).

During the summer of 1983 an outbreak of 49 cases of listeriosis occurred in Massachusetts; of the 40 cases in which serotype information was available, 32 were due to serotype 4b. Forty-two of the patients were immunosuppressed adults, while only 7 were neonates. A
case-control study was conducted and found a strong association between illness and consumption of a specific brand of pasteurized milk. Upon further investigation it was determined that some of the milk had been acquired from a farm with cows infected with *L. monocytogenes*. Questions remained as to whether some organisms had survived pasteurization or whether the milk had been reinfected with *Listeria* post-pasteurization (20).

A large epidemic involving 142 cases occurred in Los Angeles County in 1985. Ninety-three of the cases were perinatal and 49 occurred in non-pregnant adults. A case-control study was performed and linked the outbreak to consumption of Mexican-style cheese from a cheese factory that used unpasteurized milk. Serotyping and phage-typing was performed and demonstrated that 86 of the cases were of serotype 4b and 73% of these had the same phage-type. *L. monocytogenes* of the same sero- and phage-type was isolated from samples of the cheese (8). A later study showed that fecal carriage of *L. monocytogenes* in employees at the cheese plant was 9.7% and that "higher-than-normal" rates of fetal demise occurred in pregnant cheese-factory workers (21).

A population-based, case-control study conducted by the Centers for Disease Control in 1986-87, identified uncooked hot dogs and undercooked chicken as possible sources of *L. monocytogenes* infection (9). In 1989, a case-control study
of an outbreak in Philadelphia reported that cases were more likely than controls to have eaten ice-cream or salami, and were more likely to have shopped at a certain grocery store chain (22).

In 1992, a large, multi-state, case-control study of sporadic listeriosis conducted by the C.D.C. recorded diet history and obtained samples of food for culture. If a food grew *L. monocytogenes*, the serotype was compared to the serotype from the patient. The study was limited by the fact that very few food cultures were positive for *Listeria* and by the fact that the food samples obtained after the onset of illness from the study participants may not have been from the foods that caused illness. However, based on diet history, this study was able to show an association of sporadic listeriosis with consumption of soft cheeses and delicatessen foods. Eating undercooked chicken was associated with listeriosis in immunosuppressed individuals (10).

D. Nosocomial Transmission

Nosocomial transmission of listeriosis has been demonstrated. In 1975, a cluster of 7 cases among neonates in a hospital in South Carolina prompted an investigation of possible horizontal transmission of *L. monocytogenes* in the hospital. Six of the 7 infants were infected with serotype 4B. The study found a positive association of neonatal
listeriosis with low socioeconomic status of the mother and vaginitis during pregnancy, but was unable to demonstrate nosocomial transmission (23). A probable source and mode of transmission was found in an outbreak of neonatal listeriosis that occurred in a hospital in Costa Rica in 1989. A bottle of contaminated mineral oil, with which the infants were bathed, was the probable source. It was hypothesized that transmission occurred when the oil came into contact with mucous membranes or was aspirated into the lungs (24). Other reports have suggested person-to-person transmission and contaminated resuscitation equipment as sources of horizontal transmission of listeriosis in hospitals (4,25). However, the source of exposure and route of transmission in these instances were not confirmed by microbiologic or epidemiologic studies.

A hospital outbreak involving 6 renal-transplant patients was reported in 1982. Because 4 of the 6 were close associates, and all 4 were infected with serotype 1b, it was thought that transmission may have occurred via contaminated material or direct person-to-person contact. The method of transmission and source of infection remained unknown, however (26).

Route of Infection

While infection via direct skin or eye contact can occur among those exposed to infected animals, this route of
spread accounts for a tiny fraction of cases. The most likely portal of entry, in most cases, is the gastrointestinal tract. A prodrome characterized by gastrointestinal symptoms, especially diarrhea, prior to invasive L. monocytogenes infection, has been noted in several reports (4,22,27). Other reports suggest that prior or concurrent infection of the gastrointestinal tract with another pathogen can cause lesions in the gastrointestinal tract and thus allow L. monocytogenes to invade the host. In one case report, a previously healthy 57-year-old man developed listeriosis 3 weeks after an episode of documented shigellosis (28). In most cases, however, a culture-proven gastrointestinal infection due to another pathogen has not been documented. Another possibility is that L. monocytogenes infects the gastrointestinal tract and causes both diarrhea and lesions of the intestinal mucosa that allow invasive infection. Thus, it remains unclear whether the gastrointestinal symptoms that frequently precede the onset of listeriosis are due to another intestinal infection or disturbance that precedes and promotes a secondary invasion by L. monocytogenes or whether the symptoms are part of the primary infection by L. monocytogenes (1).

Other studies have demonstrated an increased risk of listeriosis in persons with reduced gastric acidity due to frequent ingestion of either H2-blockers (cimetidine and ranitidine) or antacids for peptic ulcer disease (27).
Since *L. monocytogenes* is sensitive to low pH, it has been suggested that acid secretion in the stomach has a role in preventing disease (1).

**The Clinical Syndromes**

Excluding the "early" neonatal cases (infection of the neonate in utero), meningitis is the predominant clinical syndrome in 30-55% of listeriosis cases (1). Although most bacterial meningitis is not caused by *L. monocytogenes*, one study in New York City, estimated that it was the 5th leading cause of bacterial meningitis (3). Some reports have indicated that *L. monocytogenes* is the leading cause of bacterial meningitis in cancer patients (5).

Unfortunately for the clinician, meningitis due to *L. monocytogenes* does not present with a characteristic clinical picture. Symptoms and signs can be vague and non-specific, and range from classic meningitis with nuchal rigidity, headache, and altered mental status to only mild confusion and low grade fever (1,5). Cerebrospinal fluid (csf) findings can be equally ambiguous with no elevation in leukocytes, increased leukocytes, with predominantly a lymphocytosis, or increased leukocytes with predominantly a granulocytosis. Protein in the csf can be highly elevated or close to normal and glucose can be normal or low. Gram stains are unreliable for detecting *Listeria*, but the organism is easily cultured (1,4,5). Meningitis accompanied
by bacteremia occurs more often in immunocompromised patients. The case-fatality ratio is greater for these patients than it is for those who have meningitis without bacteremia (4,5).

Focal neurological signs are occasionally seen in patients with CNS infections due to L. monocytogenes (29). Of those who survive the infection, 20% will suffer residual neurological defects, including cranial nerve palsies, hemiparesis, and monoparesis (3).

Sepsis, with or without meningitis, can also occur. Symptoms of sepsis are non-specific, consisting of chills and fever, but the diagnosis of sepsis due to Listeria is easily made by blood culture. Peripheral monocytosis accompanying L. monocytogenes sepsis in humans occurs only rarely (5).

Bacterial endocarditis is a rare clinical syndrome associated with L. monocytogenes infection. While fewer than 10 cases were reported prior to 1968, increasingly more cases have been reported since then. Patients with underlying cardiac conditions tend to be at increased risk for Listeria endocarditis (2,30). Other clinical syndromes caused by L. monocytogenes include pneumonia, pleuritis, peritonitis, ocular infections, and skin lesions (3).

Perinatal listeriosis

Two distinct clinical syndromes, corresponding with "early" and "late" neonatal infection, can occur in the
setting of perinatal listeriosis. In the "early" syndrome, the pregnant woman is infected with \textit{L. monocytogenes}, usually in the 3rd trimester. The infection in the pregnant woman is either assymptomatic or relatively mild, with flu-like symptoms predominating and more serious systemic disease occurring very rarely. However, fetal infection with subsequent fetal demise may result, producing spontaneous abortion or still-birth. It is difficult to estimate the proportion of spontaneous abortions caused by \textit{L. monocytogenes}, because cultures are not routinely taken from the gestational products (1). One study, performed in France, detected \textit{L. monocytogenes} in 1.6% of all placental and fetal cultures from pregnancies that resulted in spontaneous abortion or still-birth (1).

When infants infected with \textit{L. monocytogenes} are born alive, a unique disease, known as granulomatosis infantisepatica, can occur. This disease is characterized by multiple granulomas and abscesses throughout the brain, liver, lungs and spleen. The mortality rate for these infants is very high, approaching 100% in some studies (5). Some studies have shown that prompt antibiotic treatment of the infected pregnant woman can increase survival of the fetus (8). Other studies have shown that listeriosis during pregnancy does not always result in infection of the fetus, even when antibiotics are not given (6,8).
"Late" neonatal syndrome caused by *L. monocytogenes* occurs 1 to 3 weeks after birth. The baby is usually full-term and, as *L. monocytogenes* is not cultured from the placenta or amniotic fluid and the neonate is healthy at birth, infection probably does not occur in utero. It has been hypothesized that the mothers of these infants may be heavily colonized with *L. monocytogenes* in the intestinal or vaginal tract, and that the infant becomes infected as it passes through the birth canal. Meningitis is much more common in "late" than in the "early" neonatal syndrome (5).

In summary, *L. monocytogenes* may infect the fetus through several different routes. The most likely route of infection for the "early" neonatal cases is bacteremic seeding of the placenta (31). In "late" neonatal cases, the fetus is probably infected as it passes through the birth canal during delivery (31). Neonates can also be infected after birth, through contact with contaminated materials and colonized health care professionals (4, 24, 25).

**Diagnosis**

On Gram stain, *L. monocytogenes* can be mistakenly identified as a "diphtheroid", a common, non-pathogenic contaminant. Motility at room temperature and an ability to hemolyze blood agar should help distinguish *L. monocytogenes* from non-pathogenic diphtheroids (2, 5). Culture, however, is the gold standard for diagnosis, as *L. monocytogenes* is
easily cultured from normally sterile sites. It is generally accepted that serological tests to diagnose listeriosis are unreliable because of cross-reactions of \textit{L. monocytogenes} antigens with antigens of other organisms, including \textit{Staphylococcus sp.}, \textit{Enterococcus sp.} and \textit{Escherichia coli} (3).


treatment

The treatment of choice for listeriosis is ampicillin and an aminoglycoside antibiotic (e.g. gentamicin) (5). Some reports indicate that penicillin may be just as efficacious as ampicillin (31), although others have shown a higher failure rate with penicillin (5). Because of conflicting reports of the effectiveness of sulfamethoxazole-trimethoprim against \textit{L. monocytogenes}, it should not be considered a first-line drug (1,5,32). The third generation cephalosporins have shown little or no efficacy against \textit{L. monocytogenes}. Chloramphenicol, if given in conjunction with the penicillins, may actually interfere with penicillins action against \textit{Listeria} (31,33).
NOTES

1) Gellin BG, Broome CV. Listeriosis. JAMA, 1989; 261 (9): 1313-1320.


Additional References:


CHAPTER TWO: LISTERIOSIS IN SAN FRANCISCO, ALAMEDA, AND CONTRA COSTA COUNTY--ANALYSIS OF THE GENERAL DATA.

Methods

Existing data from the Bay Area Bacterial and Mycotic Disease Surveillance Project were used to examine demographic characteristics, clinical syndrome, and underlying medical conditions of patients with invasive Listeria monocytogenes disease. All cases that occurred between November, 1988 and June, 1992 were included. Data were abstracted from the case report forms and questionnaires from a case-control study. The methods of the original study are summarized below.

A prospective, laboratory-based surveillance project to detect invasive disease due to Listeria monocytogenes and other pathogens was established in Alameda, San Francisco and Contra Costa counties beginning in November, 1988. A case of listeriosis was defined as a positive culture of Listeria from a normally sterile site (cerebrospinal fluid, blood, peritoneal fluid, etc.). For each patient, a case report form that included demographic characteristics of the patient and the clinical syndrome produced by the Listeria infection was completed. The information for the form was obtained from the patient's physician or from the medical record. Isolates of Listeria were collected and sent to the Centers for Disease Control in Atlanta for serotyping.
Sensitivity of the active surveillance system for listeriosis was monitored by periodic laboratory audits and was found to be approximately 96%.

A case-control study was also performed to search for food exposures associated with listeriosis, to assess potential risk factors, and to describe the underlying medical conditions of the patients. Patients were interviewed and medical records reviewed to obtain the desired information.

Population data for San Francisco, Alameda, and Contra Costa counties from the 1990 census were used to calculate rates of listeriosis. The chi-square test ($X^2$) was used to evaluate observed differences in proportions (1). Ninety-five percent confidence intervals were estimated using the Taylor series expansion method (2).

Results

Between November, 1988 and June, 1992, 115 cases of listeriosis were ascertained in the 3 counties. More cases occurred in San Francisco county (45.2%) than in either Alameda (35.7%) or Contra Costa county (19.1%), and the incidence rate of listeriosis in San Francisco was more than twice the rates in the other two counties (table 1). Slightly more cases were reported for men than for women (58% male to 42% female). The distribution of cases by race showed that while a greater number of cases occurred in
whites, incidence rates were slightly higher for African-Americans and hispanics (table 2).

Most cases occurred in individuals at the extremes of age. The highest age-specific incidence rate was seen in infants in the first year of life. However, the greatest proportion of cases occurred in the over-65 age-group (28.7%) and the second highest incidence rate was seen in this group (table 3).

Table 4 shows the frequency of underlying-conditions or risk factors associated with listeriosis. One or more underlying-conditions were reported for 111 of the 115 patients. Corticosteroid treatment, HIV infection, and diabetes mellitus were listed most frequently as predisposing factors.

The serotype was determined for 89 of the 115 cases. Twenty-six of the isolates were not typed either because an isolate was unavailable for submission to the CDC or because the isolate arrived at the CDC contaminated or dead. The type most frequently seen was 4B (48%), while type 1/2B made up 26%, type 1/2A made up 19%, and types 3A or 3B accounted for 7%. The distribution of the serotypes did not vary with underlying condition or risk factor, although small numbers precluded a detailed assessment (table 5). Serotype 4B was the most prominent serotype in all three counties and in all age-groups, with two exceptions: in Contra Costa county serotype 1/2B was the predominant serotype (56%) (table 6);
and in the 18 to 34 year age-group, 1/2B was the predominant serotype (44%) (table 7). Again, the small number of cases involved after stratification precluded a detailed assessment.

The majority of cases (74%) were classified as bacteremic. Of the 34% of the patients with meningitis, half of these were also bacteremic. Other clinical syndromes included the following: endocarditis (four cases); pneumonia (five cases); and perinatal syndromes (thirteen cases— including premature delivery, amnionitis, and spontaneous abortion).

The overall case-fatality ratio was 26%. Those over 65 experienced the highest case-fatality ratio (39%), while the 35 to 49 year age-group followed closely with a ratio of 35% (table 8). A greater percentage of Asian patients died (38%), compared to 27% of whites and 16% of African-Americans, but this difference was not statistically significant (p=.34, X^2 test). Also, a lower case-fatality ratio was seen in San Francisco (21%) than in the other two counties (Alameda county (32%), Contra Costa=27%), but this also was not statistically significant (p=.23, X^2 test). Case-fatality ratios appeared lower in patients with meningitis (14%) compared to patients with bacteremia and no meningitis (31%) but this difference was not statistically significant (p=.09, X^2 test). Cases classified as having both bacteremia and meningitis experienced a case-fatality
ratio that was similar to that of patients with meningitis alone (18%) \( (p=.94, X^2 \text{ test}) \). When case-fatality was examined according to underlying condition or risk factor of the patient, the highest ratios were seen in patients with non-hematologic cancer, patients with HIV/AIDS, and patients undergoing chemotherapy (table 9).

The overall annual incidence rate of listeriosis in San Francisco was 22.0 per 1,000,000 population. However, if the cases associated with HIV-infection and AIDS were subtracted, the annual incidence rate of listeriosis in San Francisco decreased to 12.0 per 1,000,000 population, a rate closer to that seen in Alameda and Contra Costa county.

**Discussion**

The study area included a population of approximately 2.7 million people. The overall annual incidence rate of listeriosis in Alameda and Contra Costa counties (9.0 and 7.0 per 1,000,000 population, respectively) was similar to the rate estimated for the United States in 1986 (7.0 per 1,000,000 population)\(^{(3)}\). However, the annual incidence rate for San Francisco county (22.0 per 1,000,000 population) was significantly greater than the national rate \( (p < .001, X^2 \text{ test}) \). While the incidence was slightly higher in African-Americans than whites, this difference was not statistically significant \( (p=0.49, X^2 \text{ test}) \). This finding is consistent with the 1986, nation-wide study, which found
little variance in the incidence of listeriosis across race (3). The variation in incidence of listeriosis by age-group in the study population was similar to that reported elsewhere, with the highest rates occurring at the extremes of age (3-5). Annual incidence rates of listeriosis among HIV-infected and AIDS patients are reported in chapter 3.

The proportion of perinatal-cases in the study population (23%) was similar to that found in the nationwide study conducted in 1986 (27%) (3). In non-pregnant adults, similar proportions of underlying-conditions and risk factors for listeriosis appeared in the study group as compared to other studies. The one exception was that the number of HIV/AIDS-related cases was considerably higher in this study than described in other reports (3-4).

The proportion of cases in which meningitis (34%) was present was similar to that in other reports, but the case-fatality ratio for listeriosis meningitis (14%) was lower than those reported in the literature (27% to 51%) (p < .05, X^2 test) (3,6). The overall mortality ratio (26%) was consistent with the range of those previously reported (19% to 35%) (3,5).

In summary, the characteristics of cases of listeriosis in San Francisco, Alameda and Contra Costa counties are, for the most part, similar to those of cases nationwide. However, the overall annual incidence rate of listeriosis in San Francisco county is triple the national rate. The
increased incidence rate of listeriosis in San Francisco was first reported in 1992 (4). The results published at that time included the data from the first two years of the study, November, 1988 to December, 1990, and combined data with those from similar study sites around the country. That report hypothesized that the increased rate of listeriosis seen in the San Francisco study area was due to the relatively large number of HIV/AIDS-related cases (4). Furthermore, the authors stated that if the HIV/AIDS-related cases were excluded, and the overall rate for the area was recalculated, the new rate (7.6 per 1,000,000 population) approached the national rate (7.4 per 1,000,000 population) (4). Performing these same calculations using 3 1/2 years of data resulted in similar findings. Thus, it is probable that the increased overall annual incidence rate of listeriosis found in the three counties was due to the preponderance of HIV-infection and AIDS, conditions that are associated with increased risk of listeriosis.
NOTES

1) Kuzman JW: Basic Statistics for the Health Sciences, ed

2) Hennekens CH, Buring JE. Epidemiology in Medicine.

3) Gellin BG, Broome CV, Bibb WF, et.al. The Epidemiology

4) Schuchat A, Deaver KA, Wenger JD, et.al. Role of Foods
in Sporadic Listeriosis: I. Case-Control Study of Dietary

5) Ciesielski CA, Hightower AW, Parsons SK, Broome CV.
Internal Medicine, 1988; 148: 1416-1419.

6) Pollock SS, Pollock TM, Harrison MJG. Infection of the
Central Nervous System by Listeria monocytogenes: a Review
of 54 Adult and Juvenile Cases. Quarterly Journal of
Medicine, 1984; 211: 331-340.
Table 1. Frequency, Percent and Annual Cumulative Incidence Rate (per 1,000,000 population) of Cases of Listeriosis By County

<table>
<thead>
<tr>
<th>County</th>
<th>Frequency</th>
<th>Percent of cases</th>
<th>Annual Incidence Rate (per 1,000,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alameda</td>
<td>41</td>
<td>35.7%</td>
<td>9.0</td>
</tr>
<tr>
<td>San Francisco</td>
<td>52</td>
<td>45.2%</td>
<td>22.0</td>
</tr>
<tr>
<td>Contra Costa</td>
<td>22</td>
<td>19.1%</td>
<td>7.0</td>
</tr>
<tr>
<td>Total</td>
<td>115</td>
<td>100.0%</td>
<td></td>
</tr>
</tbody>
</table>
Table 2. Frequency and Annual Cumulative Incidence of Listeriosis by Race

<table>
<thead>
<tr>
<th>Race</th>
<th>Frequency</th>
<th>Percent</th>
<th>Incidence Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>62</td>
<td>53.9%</td>
<td>1.1</td>
</tr>
<tr>
<td>African-American</td>
<td>19</td>
<td>16.5%</td>
<td>1.4</td>
</tr>
<tr>
<td>Asian</td>
<td>16</td>
<td>13.9%</td>
<td>0.9</td>
</tr>
<tr>
<td>Hispanic</td>
<td>11</td>
<td>9.6%</td>
<td>1.2</td>
</tr>
<tr>
<td>Unknown</td>
<td>7</td>
<td>6.1%</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>115</td>
<td>100.0%</td>
<td></td>
</tr>
</tbody>
</table>
Table 3. Frequency and Annual Cumulative Incidence of Listeriosis by Age

<table>
<thead>
<tr>
<th>Age-group</th>
<th>Frequency</th>
<th>Percent</th>
<th>Annual Cumulative Incidence Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age Unknown</td>
<td>6</td>
<td>5.2%</td>
<td></td>
</tr>
<tr>
<td>&lt; 1</td>
<td>11</td>
<td>9.6%</td>
<td>8.9</td>
</tr>
<tr>
<td>1-4</td>
<td>1</td>
<td>0.9%</td>
<td>0.2</td>
</tr>
<tr>
<td>5-17</td>
<td>2</td>
<td>1.7%</td>
<td>0.1</td>
</tr>
<tr>
<td>18-34</td>
<td>22</td>
<td>19.1%</td>
<td>0.7</td>
</tr>
<tr>
<td>35-49</td>
<td>20</td>
<td>17.4%</td>
<td>0.8</td>
</tr>
<tr>
<td>50-64</td>
<td>20</td>
<td>17.4%</td>
<td>1.5</td>
</tr>
<tr>
<td>55+</td>
<td>33</td>
<td>28.7%</td>
<td>2.7</td>
</tr>
<tr>
<td>Total</td>
<td>115</td>
<td>100.0%</td>
<td></td>
</tr>
</tbody>
</table>
Table 4. Frequency of Underlying Conditions/ Risk Factors for Listeriosis

<table>
<thead>
<tr>
<th>Condition/Prior Factor</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroid treatment</td>
<td>26</td>
<td>18%</td>
</tr>
<tr>
<td>HIV infection/AIDS</td>
<td>23</td>
<td>16%</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>17</td>
<td>12%</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>13</td>
<td>9%</td>
</tr>
<tr>
<td>Neonate</td>
<td>13</td>
<td>9%</td>
</tr>
<tr>
<td>Renal disease</td>
<td>12</td>
<td>8%</td>
</tr>
<tr>
<td>Hematologic Cancer</td>
<td>11</td>
<td>8%</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>10</td>
<td>7%</td>
</tr>
<tr>
<td>Elderly (≥75 y.o.)</td>
<td>8</td>
<td>5%</td>
</tr>
<tr>
<td>Non-hematologic malignancy</td>
<td>3</td>
<td>5%</td>
</tr>
<tr>
<td>Alcoholism</td>
<td>7</td>
<td>3%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>144</strong></td>
<td><strong>100.0%</strong></td>
</tr>
</tbody>
</table>

**Underlying conditions/risk factors were listed for 111/115 patients. Some patients had more than 1 underlying condition, so each condition was counted separately.**
Table 5. Proportion and Percent of Serotypes of *L. monocytogenes* by Underlying Condition/ Risk Factor of the Patient

<table>
<thead>
<tr>
<th>Serotype</th>
<th>Underlying Condition</th>
<th>4B (%)</th>
<th>1B (%)</th>
<th>1A (%)</th>
<th>3B (%)</th>
<th>3A (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids</td>
<td>9/21 (43)</td>
<td>7/21 (33)</td>
<td>4/21 (19)</td>
<td>0</td>
<td>1/21 (5)</td>
<td></td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>8/20 (40)</td>
<td>6/20 (30)</td>
<td>4/20 (20)</td>
<td>1/20 (5)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>9/14 (64)</td>
<td>2/14 (14)</td>
<td>3/14 (21)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Pregnancy</td>
<td>4/9 (44)</td>
<td>3/9 (33)</td>
<td>1/9 (11)</td>
<td>1/9 (11)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Neonate</td>
<td>4/9 (44)</td>
<td>2/9 (22)</td>
<td>2/9 (22)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Renal Disease</td>
<td>7/10 (70)</td>
<td>3/10 (30)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Hematologic Cancer</td>
<td>4/10 (40)</td>
<td>4/10 (40)</td>
<td>2/10 (20)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>3/9 (33)</td>
<td>2/9 (22)</td>
<td>3/9 (33)</td>
<td>0</td>
<td>1/9 (11)</td>
<td></td>
</tr>
<tr>
<td>Elderly (&gt;75 y.o.)</td>
<td>3/5 (60)</td>
<td>1/5 (20)</td>
<td>1/5 (20)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Non-Hematologic Cancer</td>
<td>3/6 (50)</td>
<td>1/6 (17)</td>
<td>2/6 (33)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Alcoholism</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2/2 (100)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>54</td>
<td>31</td>
<td>22</td>
<td>4</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

Note: Only 89 serotypes were known, but because some patients experienced more than one underlying condition and the underlying conditions were listed separately, the total shows 113 serotypes.
Table 6. Frequency and Percent of Serotypes of *L. monocytogenes* by County

<table>
<thead>
<tr>
<th>County</th>
<th>4B (%)</th>
<th>1B (%)</th>
<th>1A (%)</th>
<th>3B (%)</th>
<th>3A (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>San Francisco</td>
<td>19 (47)</td>
<td>8 (20)</td>
<td>11 (27)</td>
<td>2 (5)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Alameda</td>
<td>19 (63)</td>
<td>5 (17)</td>
<td>6 (20)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Contra Costa</td>
<td>7 (39)</td>
<td>10 (56)</td>
<td>0</td>
<td>1 (6)</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>45</td>
<td>23</td>
<td>17</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>
Table 7. Frequency and Percent of Serotypes of *L. monocytogenes* by Age-Group

<table>
<thead>
<tr>
<th>Age-group</th>
<th>4B (%)</th>
<th>1B (%)</th>
<th>1A (%)</th>
<th>3B (%)</th>
<th>3A (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1</td>
<td>5 (56)</td>
<td>2 (22)</td>
<td>2 (22)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1-4</td>
<td>0</td>
<td>1 (100)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5-17</td>
<td>1 (50)</td>
<td>1 (50)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>18-34</td>
<td>7 (39)</td>
<td>8 (44)</td>
<td>2 (11)</td>
<td>1 (6)</td>
<td>0</td>
</tr>
<tr>
<td>35-49</td>
<td>11 (65)</td>
<td>2 (12)</td>
<td>3 (18)</td>
<td>1 (6)</td>
<td>0</td>
</tr>
<tr>
<td>50-64</td>
<td>7 (44)</td>
<td>4 (25)</td>
<td>3 (19)</td>
<td>1 (6)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>65+</td>
<td>1 (51)</td>
<td>5 (20)</td>
<td>7 (28)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>54</td>
<td>23</td>
<td>17</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Age-Group</td>
<td>Frequency of Deaths</td>
<td>Case-Fatality Ratio</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------</td>
<td>---------------------</td>
<td>---------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>1/6</td>
<td>17%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 1</td>
<td>2/11</td>
<td>18%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-4</td>
<td>0/1</td>
<td>0%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-17</td>
<td>0/2</td>
<td>0%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-34</td>
<td>1/22</td>
<td>5%</td>
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<td></td>
</tr>
<tr>
<td>35-49</td>
<td>7/20</td>
<td>35%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50-64</td>
<td>6/20</td>
<td>30%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>65+</td>
<td>13/33</td>
<td>39%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>30</td>
<td>100%</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Underlying Condition</td>
<td>Case Fatality Ratio</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------------------------</td>
<td>---------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-hematologic Cancer</td>
<td>63%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>46%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>40%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elderly (&gt;75 years)</td>
<td>38%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corticosteroid treatment</td>
<td>35%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcoholism</td>
<td>33%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>24%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal Disease</td>
<td>25%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematologic Cancer</td>
<td>18%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neonate</td>
<td>18%</td>
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</tr>
<tr>
<td>Pregnant</td>
<td>0%</td>
<td></td>
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</tbody>
</table>
CHAPTER THREE: LISTERIOSIS IN HIV-INFECTED AND AIDS PATIENTS IN SAN FRANCISCO, ALAMEDA, AND CONTRA COSTA COUNTY

Background

As noted earlier, *L. monocytogenes* rarely causes disease in healthy adults; individuals with compromised T-cell function are at increased risk. Thus, it has been expected that HIV-infected and AIDS patients, who have seriously impaired T-cell function, would be at increased risk of listeriosis. It has been estimated that the risk of listeriosis is 200 to 300 time greater for HIV-infected and AIDS patients than for the general population, indicating that the risk of listeriosis is considerably increased for HIV-infected and AIDS patients. However, the incidence of listeriosis in HIV-infected and AIDS patients is still only 1 to 2 per 1000 patients (1), and listeriosis is not considered a major opportunistic infection in these patients. In the last ten years, only 39 cases of HIV-related listeriosis have been reported in the literature.

**Why doesn't listeriosis occur more frequently in HIV-infected and AIDS patients?**

Hypotheses for why listeriosis remains a relatively infrequent complication in HIV-infected and AIDS patients have included: 1) that these patients frequently take a greater number of medications that may protect against listeriosis (e.g. antimicrobial agents); 2) that they may be
more cautious about cooking and/or avoiding high-risk foods, so that their exposure to *Listeria* is decreased; and 3) that the first line of defense against *L. monocytogenes*, mediated by lymphocyte-independent macrophage activity, is unaltered or even hyperactive in HIV-infected patients and confers protection against listeriosis (2-3). Of the arguments listed, the third has received the greatest attention in scientific literature.

As early as the 1960's, Mackaness, et.al., performed several elegant studies illustrating that *L. monocytogenes* was an intracellular parasite, and that prevention of disease was mediated through the phagocytic activity of host macrophages (4-5). Further studies elucidated the involvement of two branches of the immune response in preventing listeriosis: an early, non-specific, lymphocyte-independent, phagocytic response by non-activated macrophages; and a delayed, specific, lymphocyte-dependent response that was mediated through activated-macrophages (6-8). This model has been used in explanations for why listeriosis is not a more common disease in HIV-infected and AIDS patients, because while CD4-lymphocyte impairment in AIDS is severe, the primary phagocytic activity of macrophages and neutrophils appears unaltered. Some studies have even suggested that there is a hyperfunction of macrophage activity in HIV-infected and AIDS patients (9-10). These studies have demonstrated a link between the
increased cytotoxic activity of macrophages and abnormally high levels of tumor necrosis factor and interferon-gamma that are found in HIV-infected and AIDS patients (9-11). Thus, it has been hypothesized that these non-specific, hyperactive macrophages may be able to ward off listeriosis until the patient is severely immunocompromised or until another factor destroys the primary phagocytic line of defense. Given how common L. monocytogenes is in the foods we eat and in the environment, some combination of effects: immunological, epidemiological, pharmacological, and possibly some unknown factor is probably at work to protect HIV-infected and AIDS patients from developing listeriosis more frequently.

The literature on listeriosis associated with HIV-infection and AIDS:

Of the 39 cases of listeriosis associated with HIV-infection and AIDS described in the literature, 35 of the patients were men, 2 were women and in 2 cases the sex of the patient was not specified. The mean age was 38 years, with a range of 26 to 60 years. The risk factors for HIV infection included 20 men who were gay or bisexual, 9 injection drug-users, 1 transfusion recipient, and 1 Haitian. For 8 cases, information on the risk factors for HIV was not given. Twenty-one individuals were HIV positive, with no AIDS-defining condition, and 18 had AIDS.
Recent corticosteroid treatment (12-14), prior chemotherapy (14), prior gastrointestinal infection (3,12,14-16), consumption of unpasteurized cheese (17), and pregnancy (18) were listed as additional, non-AIDS, risk factors for listeriosis in 15 of the patients. The remaining 24 patients had no identifiable risk factors for listeriosis other than HIV positivity or AIDS. Only 14 individuals had a lumbar puncture performed, with 9 demonstrating laboratory evidence of CNS involvement (e.g. elevated leukocytes, elevated protein, and decreased glucose levels). Eleven of the patients had positive cerebrospinal fluid (csf) cultures. Over 80% of the patients had blood cultures positive for L. monocytogenes.

The majority (70%) of patients were initially treated with ampicillin alone or in combination with another antibiotic. Of those who were initially treated with a non-ampicillin antibiotic, 4 were switched to ampicillin after the culture results were known.

Seventeen of the patients had another opportunistic infection or serious medical condition concurrent with the L. monocytogenes infection. Eight individuals died and 31 patients survived their hospitalization. Among the patients who died, it was not always clear that listeriosis was the cause of death. In some cases it was possible that mortality was due to a concurrent infection or disease process other than listeriosis.
Because these 39 patients were described in 20 different reports, there was inconsistency in what information was included. History of medications taken and previous occurrence of opportunistic infections were incompletely documented. Information on CD4-lymphocyte counts and duration of time from AIDS diagnosis was often omitted. These data might help determine if listeriosis tends to occur early or late in the course of AIDS. This study was undertaken in order to draw a more complete picture of the epidemiological and clinical nature of listeriosis in HIV-infected individuals.

Methods

All cases of listeriosis in HIV or AIDS patients that occurred between November, 1988 and June, 1992 in San Francisco, Contra Costa or Alameda county were selected for this study. The selection was made from the pre-existing data set collected by the Bay Area Bacterial and Mycotic Disease Surveillance Project. The methods used by the original study to identify cases of listeriosis were described in chapter 2. Information on HIV-infection or AIDS status was obtained from the case-control questionnaire of the Bay Area Surveillance Project study.

Additional information was gathered on the cases of listeriosis in HIV and AIDS patients. A data collection
form was used to extract the following information from the patient's chart: demographic characteristics; mode of acquisition of HIV; most recent CD4 lymphocyte count prior to listeriosis and date of count; previous opportunistic infections; concurrent infections; existence of other risk-factors for listeriosis; medications taken prior to listeriosis; and clinical information (symptoms, diagnostic studies, treatment and outcome) relevant to the episode of listeriosis.

To calculate rates of listeriosis among patients with AIDS and all HIV-infected individuals, estimates of the number of persons living with AIDS and the number of HIV-infected individuals were obtained from the AIDS Office, San Francisco Department of Health and the Alameda County Health Services Agency.

A comparison group was obtained by using information from controls who were originally collected for a case-control study on Salmonella and Campylobacter infection in patients with AIDS. This study was conducted by the Bay Area Bacterial and Mycotic Surveillance project during the period of January 1, 1989 to January 15, 1991. Cases were HIV-infected men or men with AIDS who were between the ages of 20 and 59. Controls were HIV-infected or AIDS patients matched to the cases on age and medical care provider. Thus, the controls represented a convenience sample of HIV-infected and AIDS patients from the study area. Counties
included in the original study region were San Francisco, Contra Costa, and Alameda counties.

Information for the Campylobacter and Salmonella study had been gathered by interview, so all participants had to be well enough, both mentally and physically, to give informed consent and be interviewed. A standard questionnaire was used to collect information on demographic characteristics and exposure history (including recent travel, diet history and health-related behavior). In addition, medical charts were reviewed and data regarding previous opportunistic infections, CD4-lymphocyte counts, and medications were abstracted. Because the mean CD4-lymphocyte count of the Campylobacter and Salmonella control group was higher than that of the listeriosis cases, only controls with CD4-lymphocyte counts below 100 were included in the listeriosis comparison group.

Statistical comparisons were made using the chi-square test for discrete data and the Student's t-test for continuous data (19,20). Odds ratios were calculated with 95% confidence intervals estimated by using the Taylor-expansion method (20). The Mantel-Haenszel chi-square test for calculating a pooled summary relative risk was used after stratified analysis of specified variables (20).
Results

Twenty-four cases of listeriosis in HIV-infected and AIDS patients were identified. Chart reviews were done on 22 of the 24. Chart reviews were not performed for two cases because the medical record for one was unavailable and the other was not a resident of the three counties under study.

Of the 22 cases, 17 (77%) were residents of San Francisco county and 5 were residents of Alameda county. The estimated mean annual incidence rate of listeriosis among HIV-infected men was 17.3 per 100,000 in San Francisco county and 17.9 per 100,000 in Alameda county. The mean annual incidence rate for men with AIDS was 110 per 100,000 in San Francisco and 120 per 100,000 in Alameda county. There were no cases of listeriosis in HIV-infected or AIDS patients from Contra Costa county.

Twenty of the patients were men and two were women. Ages ranged from 28 to 61 years, with a mean age of 42 years. The majority of patients (77%) were white, with the remainder (23%) being African-American. Of the 22 patients, 18 were gay or bisexual men who were not injection drug users and 4 were injection drug users, one of whom was a gay man. Nineteen of the patients had had a prior diagnosis of AIDS.
The results of CD4-lymphocyte counts were found for 16 (73%) of the cases. The mean most recent CD4-lymphocyte count was 118 (median = 63), with a range of 2 to 335. The most recent CD4-lymphocyte count prior to listeriosis was obtained an average of 11.5 months prior to the Listeria infection (range < 1 to 39 months).

Fourteen (64%) of the patients had one or more additional underlying conditions or risk factors for listeriosis. Six patients had a non-hematologic malignancy, three had lymphoma, four had had chemotherapy in the three weeks prior to developing listeriosis, three were being treated with prednisone, three were alcoholic, and one had end-stage renal disease. Fifteen patients (68%) had a pre-existing inflammatory or infectious gastrointestinal disorder or gastrointestinal lesion that preceded the episode of listeriosis (table 2).

Seventeen patients had previously experienced one or more infections known to be associated with AIDS. The most commonly occurring opportunistic infections were: Pneumocystis carinii pneumonia (PCP); oral or esophageal candidiasis; Herpes simplex infection; and Cytomegalovirus disease (table 3).

Few medications were being taken by the patients in the three weeks prior to their Listeria infection. The most commonly taken drugs were prophylactic pentamidine (taken by 64% of the patients) and acyclovir (taken by 41% of the
patients) (see table 4 for other drugs taken). Other anti-retroviral medications were not commonly taken, with only 36% of the cases taking zidovudine and 9% taking ddI. None of the patients had been taking any of the following antibiotics in the three weeks prior to the onset of the Listeria infection: sulfamethoxazole-trimethoprim; ampicillin; penicillin; erythromycin; clofazamine; clorithromycin; clindamycin; azithromycin; ciprofloxacin; or rifampin.

Frequencies of presenting signs and symptoms of the episode of listeriosis are listed in table 5. The most commonly experienced signs or symptoms were fever (96%), chills (59%), nausea (59%), and diarrhea (55%). Blood cultures had been done on all patients and 19 (86%) were positive for Listeria. Lumbar puncture had been performed on 12 of the patients, with 6 (50%) of the cultures from cerebrospinal-fluid being positive for Listeria. There was no characteristic pattern of number of leukocytes or levels of protein and glucose in the cerebrospinal fluid. Ten cases had been diagnosed as having Listeria meningitis, 1 with empyema, 1 with peritonitis, and 1 with iritis. Many cases experienced a concurrent second infection with the episode of listeriosis (see table 6).

Initial empirical treatment with an antibiotic known to have some efficacy against L. monocytogenes infection (ampicillin, penicillin, sulfamethoxazole-trimethoprim, or
an aminoglycoside) was given to 13 (59%) of the cases. In 8 of the 9 remaining cases, when the results of the culture became available, treatment was changed to an appropriate antibiotic.

The overall case-fatality ratio was 46%. The case-fatality ratio for those who had received initial treatment likely to be effective against *Listeria* infection was 39%, while the case-fatality ratio for those who initially received an antibiotic likely to be ineffective was 56%. This difference was not statistically significant, however ($p=.43$, $X^2$ test). Five of the patients had a severe concurrent infection or disease process, including 2 patients with *Pneumocystis carinii* pneumonia; one with CMV pneumonitis; one with pericarditis of unknown etiology; and one with bleeding esophageal and rectal varices. The clinical syndromes experienced by the patients who died were: meningitis and bacteremia (4 cases); meningitis only (1 case); bacteremia only (4 cases); and empyema (1 case).

**Comparison group:**

The comparison group included 145 controls with known CD4-lymphocyte counts less than 100 (table 1). The mean most recent CD4-lymphocyte count for the controls was 47 (range < 1 to 100) (median= 40). The average duration of time since the most recent CD4-lymphocyte count was 6 months (range < 1 to 24 months).
Of the 145 controls, 83% were San Francisco county residents, 12% were Alameda county residents, and 5% were residents of Contra Costa county. Eighty-eight percent of the controls were whites, 9% African-American, and 3% were Asian, Native American or "other". The mean age of the comparison group was 38 years, with a range of 22 to 57 years.

The cases were not significantly different from controls by either county of residence (p = .53, X² test) or race (p = .16, X² test). However, the mean age of the cases and controls did differ significantly (mean age = 42 years vs. mean age of controls = 38 years, p < .01, Student's t-test). The case-group also included two female patients, while the comparison group was entirely male.

Due to the way in which the controls were selected, the mean most recent CD4-lymphocyte count for the controls was significantly lower than that of the patients (p < .001, Student's t-test). However, the mean duration of time since the most recent CD4-lymphocyte count was longer for the patients with listeriosis than for the controls (p < .001, Student's t-test).

**Univariate analysis:**

Several factors were found to be associated with listeriosis (table 7). The most significant findings were that listeriosis patients were more likely to have
concurrent Cytomegalovirus disease (p < .0001, $X^2$ test; OR= 11.2, 95% CI= 2.9 to 43.0) and were likely to be taking zidovudine (p < .005, $X^2$ test; OR=0.27, 95% CI= 0.09 to 0.86) than controls. Other findings were that a greater proportion of cases had had a prior diagnosis of lymphoma (p < .001, $X^2$ test; OR= 22.7, 95% CI=0.55 to 923.7) and Herpes simplex infection ( p < .0001, $X^2$ test; OR= 120, 95% CI=4.34 to 3,348). However, both of these findings must be interpreted with caution because of the very small number of patients involved (for lymphoma, 2 cells contained fewer than 5 cases and for Herpes infection, 1 cell contained fewer than 5 cases). Similarly, it was found that patients with listeriosis were more likely to be taking gancyclovir (p < .005, $X^2$ test; OR= 7.6, 95% CI= 1.00 to 58.1) or to have received chemotherapy in the three weeks prior to onset of listeriosis (p < .005, $X^2$ test; OR= 10.5, 95% CI= 1.14 to 97.0), but again, only small numbers of cases were involved (for both gancyclovir and chemotherapy, 2 cells contained fewer than 5 cases). Fourteen percent of the controls were taking an antibiotic that had some efficacy against Listeria (i.e. ampicillin, penicillin, sulfamethoxazole-trimethoprim, aminoglycosides) during the prior month, compared with none of the patients with listeriosis, but this difference did not reach statistical significance (p = .10, $X^2$ test).
Stratified Analysis:

The associations between Cytomegalovirus disease, zidovudine therapy, and listeriosis were examined by stratified analysis to evaluate the possible role of confounding. Using the Mantel-Haenszel pooled estimate for relative risk and Mantel-Haenszel chi-square test-statistic, it was determined that the protective effect of zidovudine therapy against listeriosis remained after the potential effect of Cytomegalovirus disease was taken into account. Similarly, the increased risk associated with Cytomegalovirus disease remained once the effect of zidovudine therapy was taken into account (the results are summarized in table 8).

Discussion

In many respects, the HIV-infected and AIDS patients with listeriosis in this study were similar to those reported previously in the literature. The patients were mostly gay or bisexual, white men between the ages of 28 to 61 years (mean age = 42). Most (86%) had an AIDS diagnosis. The data suggest that listeriosis occurs fairly late in the course of AIDS. The mean CD4-lymphocyte count was 118, but, it is probable that this count represents an overestimate of the CD4 count at the time of listeriosis, as the mean duration of time since the last CD4-lymphocyte measurement was relatively long (11.5 months).
The clinical signs and symptoms of listeriosis in the cases were mostly non-specific, with fever, chills, nausea, and diarrhea being the most common. Results of cerebrospinal fluid examination were similarly non-specific, with no characteristic pattern of levels of leukocytes, protein and glucose emerging. Although all but 1 of the cases were eventually treated with an antibiotic appropriate for listeriosis, 9 cases (41%) were initially treated with an antibiotic regimen unlikely to be effective against *L. monocytogenes*. Failure to give empirical treatment that is effective against *L. monocytogenes* is most likely due to the non-specific presentation of listeriosis and the low-level of suspicion many physicians have for this disease.

The case-fatality ratio was high (46%). Although the case-fatality ratio was higher for those who did not (56%), than for those who did (39%) receive initial antibiotic therapy likely to be effective for listeriosis, the difference was not statistically significant. Additionally, 67% of patients who were treated with an antibiotic unlikely to be effective against listeriosis, had another life-threatening disorder (pericarditis, severe gastrointestinal bleeding, and CMV pneumonitis) in addition to listeriosis, that probably contributed to their mortality.

Although the controls were taken from a different study, unrelated to listeriosis, their characteristics were very similar to those of the patients with listeriosis.
Cases and controls were similar with respect to county of residence and race, although cases were somewhat older than controls (mean age = 42 vs 38 years). Also, there were two women in the case group while the controls were entirely male. Controls had significantly lower mean most recent CD4-lymphocyte counts than cases; however the mean duration of time since the last CD4-lymphocyte count was twice as long for the cases as for the controls. It is probable, therefore, that the actual CD4-lymphocyte counts of the cases were lower at the time of their listeriosis episode and more similar to those of the controls. Cases and controls also had experienced similar frequencies of the complications of HIV-infection, suggesting that their exposures to pathogens and level of immunocompromised status were comparable.

Statistically significant differences between AIDS patients with listeriosis and control AIDS patients were that listeriosis patients were more likely to have had Cytomegalovirus disease (CMV), Herpes simplex infection, and lymphoma and were more likely than controls to be taking gancyclovir or chemotherapy. Conversely, controls were more likely to be taking zidovudine than were the cases. The small number of cases involved in many of these comparisons, however, led to extremely wide 95% confidence-intervals, and these values must be interpreted with caution.
Fewer patients with listeriosis than controls were taking zidovudine, despite their higher mean CD4-lymphocyte count. Zidovudine has been shown in vitro to have bactericidal activity against certain Gram-negative organisms, including *Salmonella typhimurium, Klebsiella pneumoniae, Shigella flexneri, Enterobacter aerogenes* and *Escherichia coli* and to protect against *Salmonella* infections in AIDS patients (21-23). While zidovudine has not been demonstrated to be effective against Gram-positive organisms in vitro, only a few members of the genera *Streptococcus* and *Staphylococcus* have been tested. Thus, it is plausible that zidovudine therapy might have bactericidal activity against *L. monocytogenes* and protect against listeriosis in HIV-infected and AIDS patients.

Several different factors, in addition to depleted CD4-lymphocytes, have been suggested to increase the risk of listeriosis in HIV-infected and AIDS patients. It seems likely that the gastrointestinal tract is the major site of host invasion by *Listeria* (24). HIV-infected and AIDS patients have many inflammatory gastrointestinal disease and gastrointestinal infections that may increase their risk of listeriosis (3). In this study, 15 (68%) of the cases had a preceding severe inflammatory or infectious gastrointestinal disorder or lesion. However, as data on the frequency of these conditions were not available for the control group, comparisons could not be made. Reports in the literature
have indicated that 50-70% of AIDS patients have an inflammatory or infectious gastrointestinal disorder (25-26), suggesting that the frequency of gastrointestinal disorders found in the cases in this study is not unusual for these patients.

CMV occurred in a much greater proportion of the patients with listeriosis than the controls. Although the significance of this association cannot be determined with certainty, there are several plausible explanations. First, in immunosuppressed patients, CMV can cause an inflammatory colitis with erosions and ulcerations of the intestinal mucosa (27-28). Thus, CMV might help create a "portal of entry" for Listeria invasion. In this study, only 4 of the 10 patients with CMV had diagnosed CMV colitis, while the remainder had CMV retinitis (4 cases) or pneumonitis (2 cases). CMV retinitis, however, is frequently accompanied by disseminated disease, and can be considered a sign of systemic infection (27-29). Undiagnosed CMV colitis is certainly a possibility in patients with CMV retinitis or pneumonitis who have chronic diarrhea of unknown etiology (28-29). According to one report, up to 25-30% of patients with CMV retinitis have accompanying undiagnosed CMV colitis (30). Of the patients with CMV pneumonitis or retinitis in this study, all but 2 had chronic, severe diarrhea. Thus, it is possible that CMV colitis, diagnosed or undiagnosed,
creates a portal of entry that allows for the invasion of Listeria in these patients.

Clinical and laboratory studies have demonstrated that CMV disease causes a reversible depletion of CD4-lymphocytes and an increase in the number of T-lymphocyte suppressor cells (31-32). The immunosuppressive effects of CMV disease, with a consequent increased number of bacterial infections, has been reported extensively in the organ-transplant literature (33). In one report, listeriosis was specifically mentioned as a bacterial infection associated with CMV disease (33). It is possible, therefore, that CMV disease predisposes to listeriosis by causing further impairment of the host immune system (34).

It has also been hypothesized that Listeria, like CMV, tuberculosis and some other intracellular pathogens, may infect host macrophages and then assume latency, only to be activated when the host’s immunity becomes sufficiently repressed. In this scenario, further immunosuppression caused by CMV would allow for activation of the latent Listeria infection. There is, as yet, no evidence in the literature that this occurs with listeriosis, however.

Finally, both CMV and listeriosis are opportunistic diseases known to occur in the severely immunosuppressed. Thus, it is possible that the association of CMV with listeriosis is not a causal one, but is simply a reflection of the state of host immunosuppression. This possibility is
less likely in this study because the mean CD4-lymphocyte count of the patients with listeriosis was greater than that of the controls. However, it is possible that some immune impairment not reflected by CD4-lymphocyte counts was present.

Herpes simplex infection might also increase the risk of listeriosis by causing gastrointestinal lesions and creating a portal of entry for *Listeria* infection. Herpes simplex infection can cause an ulcerating, bloody colitis in AIDS patients (27,35-36); however, anorectal lesions and proctitis are more common presentations of Herpes simplex in gay and bisexual men who have AIDS (27,35,37). Three (33%) of the 10 patients in this study had active anorectal Herpes simplex infection at the time of listeriosis. Two patients (20%) had oro-labial herpes. The site of Herpes simplex infection for 5 patients (50%), all gay or bisexual males, could not be determined from the record however, nor could it be determined whether herpes was active at the time of listeriosis infection. Five of the patients had been taking acyclovir in the three weeks prior to listeriosis, one of whom also had active anal herpes. It has been well-documented, however, that resistance to acyclovir can develop in Herpes simplex infection in patients with AIDS (27,38-39). Thus, it is possible that anorectal lesions caused by Herpes simplex infection allowed for the invasion
of *Listeria* in at least three of the patients with listeriosis.

Fourteen of the cases had one or more additional non-AIDS conditions such as lymphomas, non-hematologic cancers, chemotherapy, prednisone therapy, alcoholism, and end-stage renal disease that are known to be risk factors for listeriosis independent of HIV-infection. It is possible that the occurrence of multiple risk factors has a cumulative effect on the impairment of the immune system or reflects an increased risk for listeriosis in a way not accounted for by CD4-lymphocyte count or HIV-infection alone.

**Conclusion**

The relative rarity of listeriosis in HIV-infected and AIDS patients made it a difficult entity to study. Although this study was larger than any published in the literature, it still consisted of only 22 cases. The small numbers involved made it difficult to evaluate the possible interacting effects of different variables. Nonetheless, the results suggested an increased risk of listeriosis associated with CMV disease and a possible protective effect of zidovudine therapy against listeriosis. Furthermore, the effects of CMV disease and zidovudine appeared to be independent of each other.
In general, HIV-infected and AIDS patients who developed listeriosis tended to be severely immunosuppressed, with multiple complications of HIV-disease. Many of them had other severe disease processes or infections concurrent with listeriosis. The presenting signs and symptoms of listeriosis were non-specific, as were the characteristics of the cerebrospinal fluid analysis. The case-fatality ratio associated with listeriosis was high, but it is probable that the occurrence of multiple disease states and the severely debilitated nature of the patients contributed to their mortality. Thus, while increased education of physicians caring for HIV-infected and AIDS patients may raise the index of suspicion for listeriosis and may promote empirical treatment with an antibiotic that covers listeriosis, the effects on mortality may not be great.

The results of this study further stress the need for counselling of HIV-infected and AIDS patients on the importance of careful preparation and cooking of foods and which foods to avoid altogether. Proper food handling and preparation will not only help to protect against listeriosis, but will also help to prevent infections with other food-borne pathogens. Additional protection against listeriosis may be seen as sulfamethoxazole-trimethaprim, which has some efficacy against listeriosis, has taken the
place of pentamidine as a first-line prophylactic therapy for \textit{Pneumocystis carinii} pneumonia.

Finally, although HIV-infected and AIDS patients are at increased risk for listeriosis, it is not a common opportunistic infection in these patients for reasons that are still not well defined. Further epidemiological and laboratory studies may help to shed more light on the pathogenesis of listeriosis and may provide insights into the HIV disease process.
NOTES


Additional References:


## TABLES FOR CHAPTER THREE: DATA ON LISTERIOSIS IN HIV-INFECTED AND AIDS PATIENTS AND CONTROLS

### Table 1. Summary of Characteristics of Patients with Listeriosis and Controls

<table>
<thead>
<tr>
<th></th>
<th>Cases (%)</th>
<th>Controls (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of cases</td>
<td>22 (100%)</td>
<td>145 (100%)</td>
</tr>
<tr>
<td>County of Residence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>San Francisco</td>
<td>17 (77%)</td>
<td>120 (83%)</td>
</tr>
<tr>
<td>Alameda</td>
<td>5 (23%)</td>
<td>17 (12%)</td>
</tr>
<tr>
<td>Contra Costa</td>
<td>0</td>
<td>7 (5%)</td>
</tr>
<tr>
<td>Number of Female cases</td>
<td>2 (9%)</td>
<td>0</td>
</tr>
<tr>
<td>Mean Age (in years) (range)</td>
<td>42 (28 to 61)</td>
<td>38 (22 to 57)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>17 (77%)</td>
<td>128 (88%)</td>
</tr>
<tr>
<td>African-American</td>
<td>5 (23%)</td>
<td>13 (9%)</td>
</tr>
<tr>
<td>Asian or &quot;other&quot;</td>
<td>0</td>
<td>4 (3%)</td>
</tr>
<tr>
<td>CD4-cell count</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean (range)</td>
<td>118 (2 to 335)</td>
<td>47 (&lt;1 to 100)</td>
</tr>
<tr>
<td>median</td>
<td>67</td>
<td>40</td>
</tr>
<tr>
<td>Time since most recent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4-cell count (in months)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean (range)</td>
<td>11.5 (&lt;1 to 39)</td>
<td>6 (&lt;1 to 24)</td>
</tr>
</tbody>
</table>

67
Table 2. Frequency of Pre-existing Gastrointestinal Infections, Inflammation, or Lesions Experienced by Patients with Listeriosis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic diarrhea *</td>
<td>8</td>
</tr>
<tr>
<td>Chronic colitis</td>
<td>2</td>
</tr>
<tr>
<td>Culture-proven infection**</td>
<td>2</td>
</tr>
<tr>
<td>Rectal prolapse/ rectal bleeding</td>
<td>1</td>
</tr>
<tr>
<td>Anal herpes/ rectal bleeding</td>
<td>1</td>
</tr>
<tr>
<td>Rectal varices/ rectal bleeding</td>
<td>1</td>
</tr>
</tbody>
</table>

*the label "chronic diarrhea" was used only when the patient had severe diarrhea that required rehydration therapy or lomotil anti-diarrheal medication.

**the two culture proven gastrointestinal infections were *Clostridium difficile* and *Entamoeba histolytica*
Table 3. Previous Opportunistic Infections Experienced by Patients with Listeriosis and Controls

<table>
<thead>
<tr>
<th>Opportunistic Infection</th>
<th>Cases Frequency (%)</th>
<th>Controls Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral candidiasis</td>
<td>16 (73%)</td>
<td>99 (68%)</td>
</tr>
<tr>
<td>Pneumocystis carinii pneumonia</td>
<td>11 (50%)</td>
<td>67 (46%)</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>10 (46%)</td>
<td>10 (7%)</td>
</tr>
<tr>
<td>Herpes simplex virus</td>
<td>10 (46%)</td>
<td>1 (.7%)</td>
</tr>
<tr>
<td>Human papilloma virus</td>
<td>5 (23%)</td>
<td>*</td>
</tr>
<tr>
<td>Varicella Zoster</td>
<td>4 (18%)</td>
<td>33 (23%)</td>
</tr>
<tr>
<td>Bacterial pneumonia</td>
<td>3 (14%)</td>
<td>*</td>
</tr>
<tr>
<td>Cryptococcus neoformans</td>
<td>2 (9%)</td>
<td>9 (6%)</td>
</tr>
<tr>
<td>Mycobacterium Avium Complex</td>
<td>1 (5%)</td>
<td>8 (6%)</td>
</tr>
</tbody>
</table>

* these values were not available for the controls
Table 4. Medications Taken by Patients and Controls in the Three Weeks Prior to Onset of Listeriosis Episode

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cases Frequency (%)</th>
<th>Controls Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pentamidine</td>
<td>14 (64%)</td>
<td>86 (59%)</td>
</tr>
<tr>
<td>Acyclovir</td>
<td>9 (41%)</td>
<td>65 (46%)</td>
</tr>
<tr>
<td>Zidovudine</td>
<td>8 (36%)</td>
<td>98 (67%)</td>
</tr>
<tr>
<td>Gancyclovir</td>
<td>4 (19%)</td>
<td>4 (3%)</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>2 (9%)</td>
<td>13 (9%)</td>
</tr>
<tr>
<td>ddI</td>
<td>2 (9%)</td>
<td>9 (6%)</td>
</tr>
<tr>
<td>Dapsone</td>
<td>1 (5%)</td>
<td>12 (8%)</td>
</tr>
</tbody>
</table>
Table 5: Presenting Signs and Symptoms of Patients with Listeriosis

<table>
<thead>
<tr>
<th>Sign or Symptom</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>21</td>
<td>96%</td>
</tr>
<tr>
<td>Chills</td>
<td>13</td>
<td>59%</td>
</tr>
<tr>
<td>Nausea</td>
<td>13</td>
<td>59%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>12</td>
<td>55%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10</td>
<td>46%</td>
</tr>
<tr>
<td>Headache</td>
<td>8</td>
<td>36%</td>
</tr>
<tr>
<td>Altered Mental Status</td>
<td>8</td>
<td>36%</td>
</tr>
<tr>
<td>Stiff neck</td>
<td>5</td>
<td>23%</td>
</tr>
<tr>
<td>Abdominal Cramping</td>
<td>4</td>
<td>18%</td>
</tr>
<tr>
<td>Photophobia</td>
<td>3</td>
<td>14%</td>
</tr>
</tbody>
</table>
Table 6. Infections Occurring Concurrently with Listeriosis

<table>
<thead>
<tr>
<th>Infection</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral Candidiasis</td>
<td>12</td>
<td>55%</td>
</tr>
<tr>
<td><em>Pneumocystis carinii</em> pneumonia</td>
<td>4</td>
<td>18%</td>
</tr>
<tr>
<td>Bacterial pneumonia</td>
<td>4</td>
<td>18%</td>
</tr>
<tr>
<td><em>Mycobacterium Avium</em> Complex</td>
<td>3</td>
<td>14%</td>
</tr>
<tr>
<td>Cryptococcal meningitis</td>
<td>1</td>
<td>5%</td>
</tr>
<tr>
<td><em>Mycobacterium tuberculosis</em></td>
<td>1</td>
<td>5%</td>
</tr>
<tr>
<td><em>Mycobacterium gordonae</em></td>
<td>1</td>
<td>5%</td>
</tr>
<tr>
<td><em>E. histolytica</em> diarrhea</td>
<td>1</td>
<td>5%</td>
</tr>
<tr>
<td><em>E. coli</em> sepsis</td>
<td>1</td>
<td>5%</td>
</tr>
</tbody>
</table>
Table 7. Results of the Univariate Analysis: Factors Associated with Risk of Listeriosis

<table>
<thead>
<tr>
<th>Factor</th>
<th>Proportion of</th>
<th></th>
<th>p-value</th>
<th>Odds Ratio (95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>cases</td>
<td>controls</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I. Concurrent condition</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytomegalovirus infection</td>
<td>10/22</td>
<td>10/145</td>
<td>&lt; 0.0001</td>
<td>11.2 (2.90 to 43.0)</td>
</tr>
<tr>
<td>Herpes simplex infection</td>
<td>10/22</td>
<td>1/145</td>
<td>&lt; 0.0001</td>
<td>120.0 (4.34 to 3,348.0)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>3/22</td>
<td>1/145</td>
<td>&lt; 0.001</td>
<td>22.7 (0.55 to 923.7)</td>
</tr>
<tr>
<td>II. Medications taken in the 3 weeks prior to listeriosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zidovudine</td>
<td>3/22</td>
<td>98/145</td>
<td>&lt; 0.005</td>
<td>0.27 (0.09 to 0.86)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>4/22</td>
<td>3/145</td>
<td>&lt; 0.001</td>
<td>10.5 (1.14 to 97.0)</td>
</tr>
<tr>
<td>Gancyclovir</td>
<td>4/22</td>
<td>4/145</td>
<td>&lt; 0.005</td>
<td>7.6 (1.00 to 58.1)</td>
</tr>
</tbody>
</table>


Table 8. Results of Stratified Analysis

<table>
<thead>
<tr>
<th>Condition</th>
<th>OR cases</th>
<th>OR controls</th>
<th>$X^2_{MH}$ (p-value)</th>
<th>OR$_{MH}$ (95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMV present</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>effect of AZT</td>
<td>(4/10)</td>
<td>(6/10)</td>
<td>0.44</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>7.1 (&lt; 0.01)</td>
<td>0.32 (0.14 to 0.74)</td>
</tr>
<tr>
<td>CMV absent</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>effect of AZT</td>
<td>(4/12)</td>
<td>(92/135)</td>
<td>0.23</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AZT present</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>effect of CMV</td>
<td>(4/8)</td>
<td>(6/98)</td>
<td>15.33</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>22.6 (&lt; 0.001)</td>
<td>10.3 (3.9 to 26.8)</td>
</tr>
<tr>
<td>no AZT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>effect of CMV</td>
<td>(6/14)</td>
<td>(4/47)</td>
<td>8.06</td>
<td></td>
</tr>
</tbody>
</table>
Data Entry Form For Listeriosis Chart Review

State Id: 

1. Demographic Information:
   DOB 
   Race (C=caucasian, B=black, N=native am., A=asian, U=unknown) 
   Ethnicity (H=hispanic, N=non-hispanic) 
   Sex (M=male, F=female) 
   County of Residence (SF, AL, CC) 
   Hospid 

2. Mode of Acquisition of HIV (indicate Y/N or write in):
   -gay male 
   -IVDU 
   -transfusion 
   -other 
   -unknown 

3. T4 cell count before listeriosis (indicate Y/N or write in):
   -known 
   -most recent count 
   -date of most recent count 
   -lowest count (if known) 
   -date of lowest count (if known) 

4. Previous opportunistic infections/ AIDS associated conditions
   (indicate Y/N).
   -AIDS diagnosis 
   -PCP 
   -if yes, PCP, how many episodes 
   -date of first episode 
   -date of most recent episode 
   -Cryptococcus 
   -Oral/esophageal candidiasis 
   -MAI 
   -Toxoplasmosis 
   -Wasting syndrome 
   -Kaposi's Sarcoma 
   -Lymphoma 
   -CMV 
   -G.I. infection/diarrhea 
   -HSV 
   -HPV 
   -VZ 
   -other pneumonia (non-PCP/Crypto) 
   -AIDS dementia 

5. Concurrent Infection (indicate Y/N or write in)
   -PCP 
   -Cryptococcus 
   -Oral/esophageal candidiasis 
   -Toxoplasmosis 
   -G.I. infection/diarrhea 
   -MAI 
   -other (non-PCP or Crypto pneumonia) 

75
-other (non-Listeria) sepsis
-other

6. Indicate which of the following drugs have been taken in the three weeks prior to Listeria infection (indicate Y/N)
   -SMX-TMP
   -Clindamycin
   -Ampicillin
   -Erythromycin
   -Clofazamine (lamprene)
   -Clarithromycin
   -Azithromycin
   -Ciprofloxacin
   -Rifampin
   -Gancyclovir
   -Acyclovir
   -Dapsone
   -Pentamidine
   -Fluconazole
   -Ketoconazole
   -AZT
   -DDI
   -DDC
   -INH

7. Additional Risk Factors/Underlying Conditions (indicate Y/N)
   -Corticosteroid tx in last month
   -recent (in the last 2 weeks) g.i. infection/diarrhea
   -renal failure
   -dialysis
   -food exposure (raw milk, mexican cheese, etc.)
   -Leukemia
   -Lymphoma
   -Other Malignancy
   -Chemotherapy (in the last month)
   -SLE
   -vascular catheter
   -alcohol abuse

8. Clinical Presentation (indicate Y/N)
   -fever
   -chills
   -nausea
   -vomiting
   -headache
   -stiff neck
   -photophobia
   -mental/behavioral changes
   -diarrhea
   -abdominal cramping

9. Clinical Syndrome (Y/N or write in)
   -bacteremia
   -meningitis
   -other
10. Laboratory Data (write in values or indicate pos/neg/not done)
   - Blood culture ____ Date of bld cx ____
   - CSF culture ____ Date of csf cx ____
   - Serotype ____
   - LP done __
     - If LP done, results:
       - WBC ______
       - % monos ___
       - % PMNs ___
       - glucose ___
       - protein ___
     - other cx done __
     - if yes, other cx done:
       - site __________
       - Listeria ___
       - other pathogen ________

11. Treatment (write in).
    initial treatment __________
    secondary treatment __________

12. Outcome (indicate L=lived D=died U=unknown) __