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House: The Epidemiologic Link between Listeriosis and Ready-to-Eat Food

THE EPIDEMIOLOGIC LINK BETWEEN LISTERIOSIS AND READY-TO-EAT FOOD PRODUCTS

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Food-borne illness can be defined as any illness caused by the consumption of food that is contaminated with some disease causing agent. There are over 250 pathogens that may contaminate food and cause human disease; these pathogens are most commonly bacterial, viral, or parasitic in nature (National Center for Infectious Diseases, 2007). It has been estimated, that in the United States alone, food-borne disease causes 76 million illnesses, 325,000 hospitalizations, and 5000 deaths every year. The most concerning food-borne contaminants have only been recognized as human pathogens in the past 20 years. The leading causes of death from food-borne illness are from three known agents, *Salmonella*, *Listeria*, and *Toxoplasma*; these 3 together account for over 75% of the deaths (Mead, 1999). Of the bacterial related deaths, 28% are caused by *Listeria monocytogenes*.

Listeria monocytogenes is an aerobic, gram-positive coccobacillus that is ubiquitous in nature. It has been proposed that it is a common, but transient, colonizer of the human gastrointestinal tract but does not cause invasive disease unless certain host factors are present or the amount consumed is so extreme that the preventive barriers of the gastrointestinal tract are overwhelmed (Schlech, 2000). Host factors that make the bacteria a concern to public health are pregnancy (risk to the fetus/neonate), advanced age, and immune-suppression (Swaminathan, 2007). Individuals that fit into these categories are representing a greater proportion of the population then they did in the past. Our society has an ever increasing elderly population as the baby boomers approach retirement age. There are more people under immune-suppressive treatments (organ transplants, corticosteroids, and chemotherapy) due to advancements in medical technologies and care. Chronic disease and the HIV epidemic are increasing the numbers of immune-compromised (Schlech, 2000). All of these combine to create a greater number of people susceptible to listeriosis then there has ever been.

In the rare instances when disease from *Listeria monocytogenes* does develop in is often severe and is known as Listeriosis. The seriousness of this disease is evidenced by the hospitalization and fatality rate of cases; it has been estimated that 92% of cases require hospitalization with a 20% fatality rate (Mead, 1999). Listeriosis can manifest a variety of ways including; meningitis, rhomboencephalitis, sepsis, seizures, valve endocarditis, arterial infections, pneumonia, hepatitis, liver abscess, peritonitis, osteomyelitis, septic arthritis, or febrile gastroenteritis. If a pregnant woman becomes infected, the disease can lead to abortion, premature labor, intrauterine fetal sepsis, intrauterine fetal death and neonatal sepsis or meningitis (Schlech, 2000).

Historically, most food-borne pathogens have been controlled by processing procedures such as pasteurization or cooking. Other bacterial pathogens are usually acquired through eating raw or undercooked meat, raw milk and produce that has been contaminated. However, with *Listeria monocytogenes* the foods most often implicated both in outbreaks and in sporadic cases are considered ready-to-eat (RTE) with no

further processing. In addition to acquiring the pathogen through raw meats, raw milk and produce the disease has been traced to consumption of deli meats, pasteurized milk, and pasteurized milk products. This is due to some unique characteristics of *Listeria monocytogenes*; it is relatively resistant to acid and high salt concentrations, it grows well at refrigerated temperature (even freezing), it persists in the environment, and it readily produces a biofilm that helps it to survive in food production facilities (Swaminathan, 2007). A 1986 survey of 41 meat-processing plants cultured samples from cleaning aids, wash areas, sausage peelers, and food contact surfaces. One-third of the plants cultured positive for *Listeria* species (American Meat Institute, 1987). The purpose of this literature review is to study the epidemiologic evidence relating contaminated ready-to-eat food products to the development of Listeriosis.

REVIEW OF STUDIES

PASTEURIZED MILK AND MILK PRODUCTS

Fleming (1985) conducted two case-control studies of patients involved in a 1983 outbreak of Listeriosis that affected 49 people. The first case-control study had 19 cases and 38 controls. Two controls were used for each patient matched by age, sex and location of residence. The study generated the conclusion that cases were more likely than controls to have consumed whole or 2% milk with a brand from one particular food store chain. The researchers recognized that using 'healthy' controls could have impacted the results and conducted a second case-control study, this time matching controls (one per case) by age and underlying medical condition. A total of 40 cases were enrolled, this time with an equal number of matched controls. The results supported the original findings; that cases were more likely to consume whole or 2% milk from one particular food store chain. In addition it was noted that there appeared to be a dose-response effect. A limitation that was not addressed in this study was recall bias; the matched controls did not experience illness and were probably not as likely to remember what they had consumed during the specified time frame. This study led to investigations of the milk processing plant by the Food and Drug Administration. The investigations were conducted both before and after the processing plant was notified of a possible contamination problem. The facility was found to be "clean, modern, and well run." No source of contamination after pasteurization was identified and no inefficiencies in pasteurization were found. This leads to the possibility that *Listeria monocytogenes* survived the pasteurization process and continued to grow during refrigeration.

Dalton (1997) conducted a case-control study involving persons who developed gastroenteritis after attending a picnic in Elizabeth, Illinois on July 9th, 1994. Attendees complained of poor quality and taste of pasteurized chocolate milk. These complaints led to sampling of leftover milk where *Listeria monocytogenes* was cultured. Infection with *Listeria monocytogenes* has only recently been associated with fever and gastrointestinal illness in the absence of severe invasive disease. This outbreak was also unique in that none of the cases had chronic illness or immune deficiencies that would predispose them to development of Listeriosis. Perhaps this feature prevented the development of the severe invasive disease. Eighty-nine percent (82 people) of picnic attendees were

House: The Epidemiologic Link between Listeriosis and Ready-to-Eat Food interviewed. Sixty of the 82 attendees interviewed reported consuming the chocolate milk. Of the sixty chocolate milk drinkers, 45 developed illness that met the case definition. This indicated a relatively high attack rate, 75% for chocolate milk consumers. In addition to the 45 defined cases, nine people had illness the week after the picnic that did not meet the case definition. These additional nine people would have raised the attack rate to 90% if they in fact did have Listeriosis. There were no cases of disease in individuals who did not drink chocolate milk; therefore, consumption of chocolate milk was implicated as the risk factor for disease development. This risk factor did not appear to be dose dependent. Confounders and biases were not specifically addressed in this article. A recall bias can be assumed due to the fact that attendees remember poor taste and quality of the chocolate milk which led to sampling and culture. Overall this was an interesting article addressing the development of gastroenteritis in healthy, non-immunocompromised adults; indicating that Listeriosis is not solely a disease of pregnancy or immunocompromised people. Confounding variables and biases should have been addressed better and controlled for if possible.

Listeria monocytogenes can be found in cattle and unpasteurized dairy products but has not often been found in butter produced from pasteurized milk. Lyytikäinen (2000) investigated an outbreak of Listeriosis in a tertiary care hospital in Finland. The serotype was unusual and had been identified in a Finnish dairy 2 years previously. Environmental sampling at the hospital isolated the outbreak strain of *Listeria monocytogenes* in all pasteurized butter samples taken. This study was a matched case-control where 3 control subjects were chosen for each case patient. There were 25 case patients and 75 control patients interviewed. The controls were hospitalized within 1 month of the cases and were matched by age, underlying conditions and hospital ward. Case patients had a higher overall consumption of butter. Biases and limitations were not specifically addressed in this study. Selection bias existed in that butter was assumed to be the causative agent and patients were asked specifically about this food item. In addition a recall bias may exist; cases are more likely to remember eating butter than controls since the controls did not experience a similar illness during that time. Researchers were able to control a confounder, susceptibility to infection, by utilizing non-affected patients who presumably had similar immune status as the controls from the same underlying condition.

READY-TO-EAT MEAT PRODUCTS

A study by de Valk (2001) discussed two unrelated outbreaks of Listeriosis in France. A case-control study was completed on the second outbreak. Cases were defined as a resident of France where the outbreak strain of *Listeria monocytogenes* was isolated between November 12, 1999 and February 28, 2000. Sporadic cases (not associated with either outbreak) of Listeriosis diagnosed between November 28, 1999 and March 1, 2000 were used as control subjects. There were 29 cases and 32 controls enrolled in this study. Case patients were significantly more likely to have eaten at least one meat product purchased from a delicatessen counter. The most commonly recognized item was jellied pork tongue but other products were also observed. The product manufacturer and a particular delicatessen counter were never isolated. This outbreak led

to the discouragement of eating one particular food item (jellied pork tongue). There were several limitations identified in the study. There was a selection bias that was addressed by only using patients that were interviewed before they knew their status as a case or a control. Recall bias was reduced by using sporadic cases as controls, everyone enrolled in the study had the disease so should remember equally as well what they ate. The biggest limitation was the extended exposure time (2-months) which led to the difficulty in identifying and tracing the origin of the contaminated food. This study did a good job of addressing the limitations and biases involved. While a particular item was never implicated it does show that an outbreak was associated with an uncommonly recognized route; processed meat products.

A case-control study was conducted by Gottlieb (2006) to identify the contaminated food that resulted in a US outbreak involving cases of Listeriosis in 9 states. Cases were defined as individuals who had positive cultures for the outbreak strain of *Listeria monocytogenes* between July 1, 2002 and November 30, 2002. Controls were individuals, from the same states as cases, who were culture positive for a non-outbreak associated strain during the same time frame. The sample size was 38 case patients and 53 control patients. Consumption of pre-cooked turkey products sliced at the deli counter of groceries and restaurants was strongly associated with the case patients. Confounders and biases were not addressed specifically in this study. One method of bias readily identifiable by the reader was recall bias; which was addressed in this study by using sporadic cases as controls, as demonstrated in the study by de Valk et al. This study did a good job of identifying the risky food item and where it originated. Results of the study led to plant disinfection and a huge recall that may have prevented a large number of additional cases.

Schwartz conducted a population-based case control study of risk factors for sporadic Listeriosis (1988). This was the earliest study found investigating sporadic cases versus outbreaks. There were 82 cases enrolled in the study that were each matched to 2-4 controls by underlying disease, age, and using the same doctor (geographic area and socioeconomic status were presumed the same based on doctor recommendation). Perinatal cases were matched by approximate date of conception. The study questionnaire asked specifically about certain foods with known risk factors; eggs, dairy products, raw fruits and vegetables, and meat and poultry products. After European reports of possible processed and pickled meat contamination; these items were added to the questionnaire. The study found two foods that were risk factors; uncooked hotdogs and undercooked chicken. Cases were 6.1 times more likely than controls to have consumed uncooked hotdogs. The study also evaluated the underlying medical condition. Pregnancy was the greatest; followed by cancer, diabetes, renal disease and kidney disease. The study identified numerous biases and attempted to control for them. One bias identified was the lack of completeness in surveillance and case representation; after reviewing it was found that cases enrolled in the study were similar to non-enrollees in all factors except race. Discharge diagnosis was 93% accurate. Surrogate interviews could have affected the results and was addressed by using multivariate analysis. The cases and controls in LA County were interviewed differently; researchers assessed the risk factors with and without these individuals and found no difference. Recall bias

House: The Epidemiologic Link between Listeriosis and Ready-to-Eat Food may have been a problem both with controls and with cases. Interviewer biases were controlled for by using blinded interviewers who asked a structured questionnaire with only yes/no answers allowed. This study did a good job of reporting limitations and addressing them. It was also able to identify an unsuspected source of infection, ready-to-eat hotdogs. However it did not identify the cause of all sporadic cases and noted that further research needs to be done to determine additional risky foods.

ADDITIONAL SOURCES OF INFECTION

Listeriosis is more commonly associated with sporadic cases than outbreaks. These cases often go without investigation due to the fact that they only affect one person. Varma's case control study focused on sporadic cases versus those cases from an outbreak (2007). Cases were defined as patients with isolated *Listeria monocytogenes* in all or part of 9 specific states (those utilizing FoodNet surveillance). There were 169 cases and 376 controls enrolled in the study. Controls were matched to cases by state, age, and immunosuppressant status. This study was unique in that it identified previously unrecognized foods as the agent; melons and hummus prepared at commercial establishments. Numerous limitations were identified in the study. Information biases due to long exposure period, use of surrogate respondents, and limited recall are all possible confounders. Selection biases were noted due to failure to enroll deceased patients as cases. Another selection bias existed in that controls were selected from physician practices. Recall biases may also have occurred since controls did not experience Listeriosis. Failure to recognize an outbreak could have skewed the results; the study addressed this issue by analyzing samples to establish that each case was unique.

SUMMARY AND CONCLUSIONS

Listeriosis is a serious food-borne illness that can be fatal if is not treated appropriately. The causative agent, *Listeria monocytogenes*, is ubiquitous in nature and therefore cannot be completely eliminated from the environment that food is produced in. Even though we cannot prevent the pathogen itself, it is possible to prevent the development of Listeriosis disease. The first step would be to recognize the most common sources of exposure to *Listeria monocytogenes*. The studies discussed in this paper have provided enough proof to implicate several uncommon sources of exposure. Through well conducted, epidemiologic studies, appropriate research, sampling of implicated food items and culturing the pathogen in processing plants, the conclusion that *Listeria monocytogenes* can be transmitted from ready-to-eat meat products, pasteurized milk and milk products, and produce is well supported. Since the pathogen cannot be removed from the environment it is important to focus on preventing the development of disease. Three prevention measures have been suggested; control the organism in the food processing environment, emphasis preparation and choice of foods at the household level, and in special circumstances (nonspecific febrile illness during pregnancy and in patients with advanced HIV infection) consider antibiotic prophylaxis (Schlech, 2000). These same basic principles can be applied to other food-borne infections; recognize the food source, control the processing environment, good hygiene

and decision making at the consumer level, and special consideration in individuals with known risk factors.

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