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Risk factors for mortality in non-pregnancy-related listeriosis

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SUMMARY

We examined non-pregnancy-related listeriosis cases in England and Wales reported to the Health Protection Agency between 1990 and 2009 ($n=1864$) using unconditional multivariate logistic regression analysis to identify factors independently associated with mortality. A subset analysis of cases between 2005 and 2009 ($n=694$) investigated the additional effect of antibiotic therapy on survival. In these cases particular malignancies, alcoholism, cardiovascular disease, increasing age, and treatment to reduce gastric acid secretion were positively associated with mortality. The absence of a concurrent condition and presence of autoimmune disease had a protective effect. The subset analysis identified illness in winter or spring as a risk factor and antibiotic therapy as a protective factor for mortality. The impact of antibiotic therapy, seasonality and reduced gastric acid status on survival should be further investigated. Policy-makers and clinicians need to more broadly advise those at risk of contracting this disease and dying as a consequence.

Key words: Epidemiology, *Listeria*, surveillance.

INTRODUCTION

Listeriosis is a rare but severe foodborne disease caused by infection with the Gram-positive bacterium *Listeria monocytogenes*. This organism is widely distributed in animal intestines and the environment and, consequently, can readily enter the food chain and persist in food production environments. Minimally processed foods stored for prolonged periods at refrigeration temperatures pose the greatest risk to consumers because of the psychrotrophic nature of this organism. Clinically, listeriosis presents as septicaemia, meningitis, meningoencephalitis, febrile gastroenteritis, miscarriage or stillbirth. Older people, those with concurrent pathologies and pregnant women and their newborns are most often affected. Non-pregnancy-related listeriosis is associated with a high case-fatality rate, with rates of between 19% and 44% reported [1–6].

The epidemiology of listeriosis in England and Wales has changed with a substantial increase in the number of cases per year during the periods 2001–2004 compared to 1990–2000 [1]. Most of this

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increase occurred in cases aged >59 years presenting with bacteraemia in the absence of central nervous system (CNS) involvement. Current data show that this increase has continued, with an average of 192 cases reported annually between 2001 and 2009 *vs.* 110 cases between 1990 and 2000 [Health Protection Agency (HPA), unpublished data). An assessment of whether this changing epidemiology has altered disease severity and hence impact has not yet been made.

We aim to report on the severity of infection with *L. monocytogenes* and identify factors that increase the likelihood of death in listeriosis cases. The identification of such factors is likely to have implications for current and future public health policy.

METHODS

National surveillance of listeriosis in England and Wales is coordinated by the HPA, Colindale. Cases of listeriosis are ascertained by the referral of putative *L. monocytogenes* isolates from clinical microbiology laboratories for confirmation and subtyping [7, 8] and/or the electronic reporting of laboratory-confirmed *L. monocytogenes* infections from these same laboratories. Data from these surveillance sources are combined, stored in a Microsoft Access database and any duplicate listeriosis cases removed. Standardized clinical data and epidemiological data (covering exposures in the 30 days before illness) are requested from local laboratories and health protection teams, respectively [9]. Data are requested again if not received within 2 months. Mortality data, captured on the clinical questionnaire, are augmented, as appropriate, with weekly death notification returns compiled by the Office of National Statistics (ONS).

Cases of listeriosis, defined as patients with compatible illnesses from whom *L. monocytogenes* was isolated from normally sterile sites, are classified further as either pregnancy-related (a maternal-fetal or maternal-neonate pair, with such pairs considered a single case) or non-pregnancy-related (those aged >1 month). For this study, a cohort of non-pregnancy-related cases of listeriosis reported in England and Wales between 1990 and 2009 were investigated. This study population was further limited to those for whom a clinical questionnaire was returned and death status was known.

Data were manipulated and analysed in Stata version 11 (Stata Corporation, USA). Proportions were compared using the χ^2 test and the χ^2 test for linear trend. Reported patient death was defined as the outcome of interest, with patients who died recorded as 'case patients' and those who survived recorded as 'control patients'. A study date was calculated for each patient based on onset, specimen or isolate receipt date as available, and this date was used to define year and season [coded to compare spring (March–May) with summer (June–August), autumn (September–November) and winter (December–February)] of illness. The lag time to clinical investigation was calculated from onset to first specimen collection or admission date as available, and this was grouped as either as ⩽1 day, or ⩾2 days based on a median of 1 day. Serogroup was coded to compare cases infected with serogroup 1/2 with those infected with serogroup 4. Gender was coded to compare males with females. Patient age was coded to compare those aged <60 years with those aged 60–69 years, 70–79 years and ⩾80 years. Patient ethnicity (name-based classification [10]) was coded to compare 'ethnic' patients with 'non-ethnic' patients. Quintiles of increasing neighbourhood deprivation were calculated by linking patients' postcodes with published indices of multiple deprivation (IMD) in England [11] and Wales [12] and grouping. Patients' infection sites were coded to compare CNS infections [*L. monocytogenes* isolated from cerebrospinal fluid (CSF) or brain tissue, clinical evidence of infection of this organ, or both] or bacteraemia in the absence of CNS infections (*L. monocytogenes* isolated from blood but not from CNS and without clinical evidence of CNS infection) with infections affecting other sites. Initially, binary variables were created to compare patients in concurrent condition subgroups (malignancies, cardiovascular diseases, etc.) with those patients with none. Malignancies were assigned an International Classification of Diseases, 10th Revision (ICD-10) [13] code while other conditions were stratified into non-systematically identified groups. Analyses of these variables revealed that most subgroups were associated with an increased risk of death (see Supplementary Table S1, available online). Given that most (81%) of this cohort of listeriosis cases had at least one known concurrent condition and this study aimed to identify the most important concurrent conditions in terms of mortality, the variables were re-coded to compare each concurrent condition subgroup with all other conditions. Finally, variables were created to distinguish cases taking immunosuppressive, cytotoxic or steroidal drugs from those who did not, and those taking medication which led to reduced gastric acid secretion.

The effect of these exposures on the outcome of interest was examined initially by calculating Mantel–Haenszel odds ratios (OR) and corresponding 95% confidence intervals (CI). Unknown and missing data were ignored during univariate analysis. Multivariate analyses were subsequently employed to control for potential confounding and to assess the independency of effects. $P \leqslant 0{\cdot}05$ was considered to be statistically significant and was used as a cut-off point for inclusion in an unconditional multivariate logistic regression model. Because of the large number of concurrent conditions significantly associated with mortality in the univariate analysis, a categorical variable was built to represent these in the multivariate model. Utilizing non-significant conditions as the reference group and retaining those patients without a concurrent condition as a distinct category, conditions were added based on ascending prevalence of these conditions in the study population. Variables found to be no longer significant during construction were re-coded to the 'other conditions' reference category. The multivariate model was simplified by using a step-down approach, with variables dropped sequentially and tested for significance using the likelihood ratio test. Unknowns and blanks for all variables included in the model were coded accordingly and retained. Effect modification between age group, concurrent conditions, received treatments, and season were assessed.

Subset analysis, 2005–2009

From 2005 onwards, the clinical questionnaire was revised to collect details of antibiotic treatment. These data were coded to compare cases who received no antibiotic therapy with those receiving empirical therapy with antibiotics without anti-listerial activity only, those receiving empirical therapy with antibiotics with anti-listerial activity only, and those receiving a combination of antibiotics with and without anti-listerial activity. It was assumed that this latter group was started on empirical therapy with antibiotics without anti-listerial activity and switched to a targeted therapy once the laboratory result was confirmed but it may well include individuals who were allergic to certain antibiotics with anti-listerial activity. Antibiotics described as having anti-listerial activity or being recommended for the treatment of symptoms indicative of *L. monocytogenes* infection were ampicillin, amoxicillin, co-amoxiclav, gentamicin, piperacillin-tazobactam, meropenem, teicoplanin, imipenem, and erythromycin [14], although some are more commonly used than others. Cases with blank returns were coded as unknowns. The analysis, as described above, was repeated using this subset to investigate the effect of antibiotic treatment on mortality between 2005 and 2009.

RESULTS

Study population

Between 1 January 1990 and 31 December 2009, 2488 laboratory-confirmed non-pregnancy-related cases of *L. monocytogenes* infection were reported in England and Wales. Of these cases, 1984 (80%) had a returned clinical questionnaire and 1864 also had available mortality data. Thirty-two (1·7%) cases reported during this period were linked to recognized outbreaks.

Clinical questionnaire receipt was independent of age or gender (χ^2 test, $P = 0{\cdot}955$ and $P = 0{\cdot}303$, respectively) and there was no change in questionnaire receipt rate during the study period (χ^2 test for trend, $P = 0{\cdot}079$). Of cases for whom a clinical questionnaire was received, mortality data availability was independent of age and gender (χ^2 test, $P = 0{\cdot}197$ and $P = 0{\cdot}965$, respectively), and these data became more complete during the study period (χ^2 test for trend, $P < 0{\cdot}001$).

Of the 1864 cases with mortality data available on a returned clinical questionnaire, the overall case-fatality rate for the study period was 41% (annual range 30–54%, Fig. 1). Compared to the period 1990–2000, the risk of *Listeria*-related mortality from 2001–2009 decreased [relative risk (RR) 0·84, 95% CI 0·75–0·93, $P = 0{\cdot}0017$] and reported mortality decreased over time (χ^2 test for trend, $P = 0{\cdot}013$). However, the average annual number of deaths from 2001 to 2009 ($n = 130$) far exceeded that observed from 1990 to 1999 ($n = 63$) (Fig. 1). Of the listeriosis cases with known mortality and age data, 74% were aged >60 years. Of those with a known concurrent condition status, 87% had a concurrent condition and, of these, 28% reported multiple conditions. The breakdown of concurrent conditions in this cohort is displayed in Supplementary Table S1 (available online).

Univariate analysis

Cases that died were no different from those that survived in terms of gender, season and increasing

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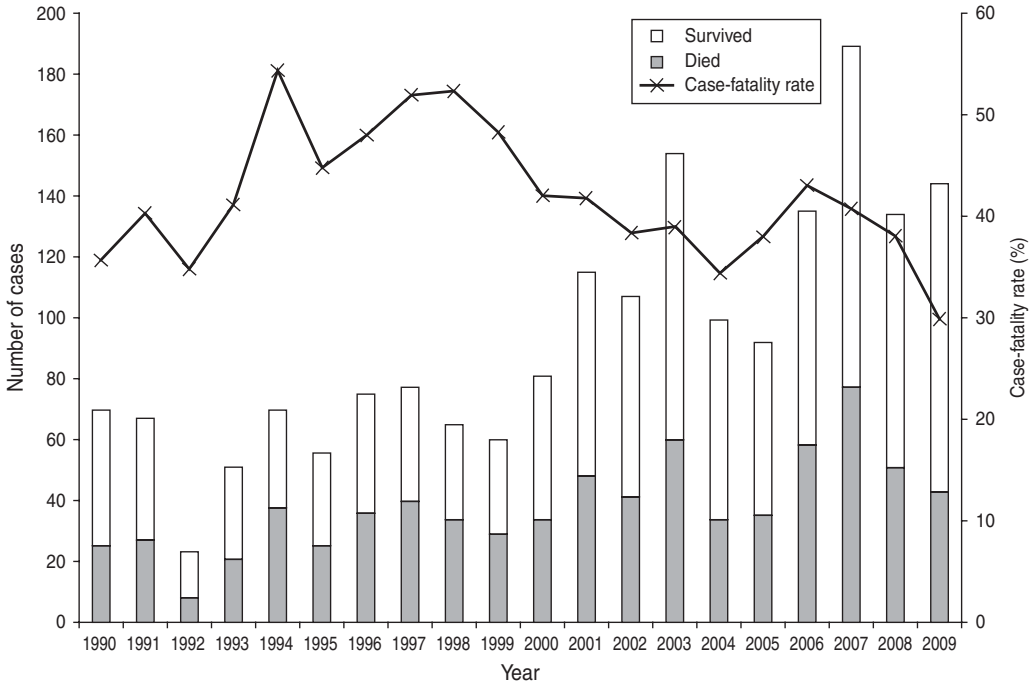

Fig. 1. Number of cases of non-pregnancy-related listeriosis with a returned clinical questionnaire and available mortality data by mortality outcome and corresponding case-fatality rate, England and Wales, 1990–2009.

neighbourhood deprivation but they were more likely to be aged >60 years and less likely to be from an ethnic minority (Table 1). There was no difference between these groups in terms of infecting *L. monocytogenes* serogroup, or the period between onset of symptoms and clinical investigation, but cases that died were more likely to have an infection that involved the CNS or bacteraemia only rather than infection elsewhere. Cases that died were more likely to have a malignant neoplasm, specifically those of respiratory and intrathoracic organs, breast, other known and those of uncertain or unknown behaviour, cardiovascular disease, or alcohol-related conditions than those that survived. However, they were less likely to have no reported concurrent condition; malignant neoplasms of lymphoid, haematopoietic, and related tissues; autoimmune disease; or recently had an operation. Furthermore, cases that died were no more likely to suffer from a malignant neoplasm of the digestive organs, renal or liver disease, diabetes or a condition that did not fall into any other category. They were also more likely to have received treatment to reduce gastric acid secretion compared to those that did not die but no more likely to have been prescribed cytotoxic drugs, steroids or immunosuppressive therapies.

Multivariate analysis

On constructing the concurrent conditions categorical variable, the following were no longer significant and were re-coded to the 'other conditions' reference category: post-operative status, and malignant neoplasms of lymphoid tissues and other known sites (OR 0·6, 95% CI 0·3–1·2, $P=0·118$; OR 0·9, 95% CI 0·7–1·3, $P=0·687$; OR 1·5, 95% CI 0·95–2·5, $P=0·081$, respectively). Multivariate logistic regression analysis revealed that when the effects of concurrent conditions, presentation site, age and treatment to reduce gastric acid secretion were considered together, ethnicity was no longer significant (OR 0·9, 95% CI 0·6–1·4, $P=0·695$) (Table 2). All strata of the concurrent conditions categorical variable were positively associated with *Listeria* mortality in the final model with the exception of 'no conditions' and autoimmune disease which were both negatively associated. Presentation site, reduced acid secretion status and age remained independently associated with mortality. There was an increasing effect with increasing age. A significant interaction between liver disease and cytotoxic drugs was identified but there was only one case with both these exposures and it was not investigated further.

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Table 1. *Factors affecting death in cases of* L. monocytogenes *infection in England and Wales, 1990–2009** (*column percentages*) (*n* = *1864*)

Variable	No. (%) of cases		OR (95% CI)	*P* value
	Died (*n* = 764)	Survived (*n* = 1100)		
Age (yr)				
<60	137 (18)	343 (31)	1·0	—
60–69	167 (22)	253 (23)	1·7 (1·2–2·2)	<0·001
70–79	234 (31)	281 (26)	2·1 (1·6–2·7)	<0·001
⩾80	208 (27)	204 (19)	2·6 (1·9–3·4)	<0·001
Not known/recorded	18 (2)	19 (2)		
Ethnicity				
Non-ethnic minority	712 (93)	996 (91)	1·0	—
Ethnic minority	50 (7)	102 (9)	0·7 (0·5–0·97)	0·035
Not known/recorded	2 (<1)	2 (<1)		
Presentation site				
Not CNS or bacteraemia	10 (1)	50 (5)	1·0	—
CNS	196 (26)	281 (26)	3·5 (1·7–7·1)	<0·001
Bacteraemia only	556 (73)	767 (70)	3·6 (1·8–7·2)	<0·001
Not known/recorded	2 (<1)	2 (<1)		
Concurrent condition (*vs.* all other concurrent conditions)				
No concurrent condition	55 (7)	177 (16)	0·4 (0·3–0·6)	<0·001
Concurrent condition	665 (87)	852 (77)	—	—
Malignant neoplasms	331 (43)	350 (32)	1·4 (1·2–1·7)	0·001
Lymphoid, haematopoietic, and related tissues	118 (15)	187 (17)	0·8 (0·6–0·99)	0·043
Digestive organs	42 (5)	54 (5)	1·0 (0·7–1·5)	0·986
Respiratory and intrathoracic organs	45 (6)	23 (2)	2·6 (1·6–4·4)	<0·001
Breast	31 (4)	17 (2)	2·4 (1·3–4·3)	0·003
Other known†	50 (7)	43 (4)	1·5 (1·01–2·3)	0·046
Uncertain or unknown behaviour‡	45 (6)	26 (2)	2·3 (1·4–3·8)	0·001
Autoimmune diseases	85 (11)	184 (17)	0·5 (0·4–0·7)	<0·001
Cardiovascular diseases	121 (16)	114 (10)	1·4 (1·1–1·9)	0·010
Respiratory diseases	42 (5)	36 (3)	1·5 (0·97–2·4)	0·067
Immunological diseases	20 (3)	38 (3)	0·7 (0·4–1·2)	0·143
Renal diseases	68 (9)	78 (7)	1·1 (0·8–1·6)	0·483
Alcoholism	51 (7)	39 (4)	1·7 (1·1–2·7)	0·011
Liver diseases	66 (9)	65 (6)	1·3 (0·9–1·9)	0·114
Diabetes	44 (6)	79 (7)	0·7 (0·5–1·02)	0·060
Post-operative status	24 (3)	54 (5)	0·6 (0·3–0·9)	0·017
Other conditions	77 (10)	111 (10)	0·9 (0·6–1·2)	0·395
Condition not described	11 (1)	6 (1)	2·4 (0·9–6·2)	0·081
Not known/recorded	44 (6)	71 (6)		
Treatment to reduce gastric acid secretion				
No	131 (17)	259 (24)	1·0	—
Yes	87 (11)	107 (10)	1·6 (1·1–2·3)	0·008
Not known/recorded	546 (71)	734 (67)		

OR, Odds ratio; CI, confidence interval.

* Mantel–Haenszel odds ratios; only categories with significant findings are presented.

† Eye, brain and other parts of the CNS; male genital organs; urinary tract; female genital organs; bone and articular cartilage; skin; thyroid and endocrine glands; lip, oral cavity or pharynx; mesothelial and soft tissues; and multiple malignancies.

‡ Ill-defined, secondary and unspecified neoplasms, or those of uncertain or unknown behaviour. The latter may not be malignant.

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Table 2. *Factors independently associated with mortality in cases of* L. monocytogenes *infection, England and Wales, 1990–2009* ($n=1984$)*

Variable	OR (95% CI)	*P* value
Concurrent conditions		
No concurrent condition	0·4 (0·3–0·6)	<0·001
Other concurrent condition (not listed below)	1·0	—
Malignant neoplasm (Mal. neo.) of the breast	3·2 (1·7–6·2)	<0·001
Mal. neo. of respiratory and intrathoracic organs	3·9 (2·2–7·1)	<0·001
Mal. neo. of uncertain or unknown behaviour†	2·5 (1·5–4·3)	0·001
Alcoholism	2·7 (1·6–4·3)	<0·001
Cardiovascular diseases	1·4 (1·01–1·9)	0·044
Autoimmune diseases	0·7 (0·5–0·96)	0·028
Not known/recorded	0·8 (0·5–1·2)	0·316
Presentation site		
Not as CNS infections or bacteraemia	1·0	—
CNS	4·4 (2·1–9·1)	<0·001
Bacteraemia only	3·2 (1·6–6·6)	0·001
Not known/recorded	5·1 (0·6–41·4)	0·126
Age (yr)		
<60		
60–69	1·6 (1·2–2·2)	0·001
70–79	2·3 (1·7–3·0)	<0·001
⩾80	3·1 (2·3–4·2)	<0·001
Not known/recorded	2·6 (1·3–5·3)	0·008
Treatment to reduce gastric acid secretion		
No	1·0	—
Yes	1·6 (1·1–2·3)	0·021
Not known/recorded	1·4 (1·1–1·8)	0·005

OR, Odds ratio; CI, confidence interval.
* Multvariate logistic regression.
† Ill-defined, secondary and unspecified neoplasms, or those of uncertain or unknown behaviour. The latter may be non-malignant neoplasms.

Subset analysis, 2005–2009

Between 2005 and 2009, 694 laboratory-confirmed cases of listeriosis with both a returned clinical questionnaire and mortality status were reported. Of these reported cases, 38% ($n=264$) died. As with the complete dataset, malignant neoplasms of the breast, respiratory and intrathoracic organs and of uncertain or unknown behaviour, and alcoholism increased the risk of mortality in both the univariate and multivariate analyses (Tables 3 and 4, respectively). Diabetes and treatment to reduce gastric acid secretion were found to have a significant effect on mortality in the univariate analysis (Table 3) but not in the final multivariate model (Table 4). Furthermore, compared to those who received no antibiotics, all antibiotic classes (empirical therapy with antibiotics with anti-listerial activity only, empirical therapy with antibiotics without anti-listerial action only, and therapy with both antibiotics with and without anti-listerial action) were negatively associated with mortality in the univariate analysis (Table 3). No difference in risk was observed between the different antibiotic classes used. This effect remained when examined alongside concurrent conditions and increasing age, which was also independently associated with mortality (Table 4). Season also exerted an independent effect on mortality, with proportionally more deaths reported in winter/spring than summer/autumn.

DISCUSSION

Principal finding

We have examined a 20-year cohort of non-pregnancy-related *L. monocytogenes* cases to identify factors independently associated with mortality. Certain malignant neoplasms, alcoholism, cardiovascular disease, increasing age, and treatment to reduce gastric acid secretion were positively associated with mortality. While there was no difference in terms

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Table 3. *Factors affecting death in cases of* L. monocytogenes *infection in England and Wales, 2005–2009** (*column percentages*) (*n* = *694*)

Variable	No. (%) of cases		OR (95% CI)	*P* value
	Died (*n* = 264)	Survived (*n* = 430)		
Age (yr)				
<60	43 (16)	120 (28)	1·0	—
60–69	65 (25)	113 (26)	1·6 (1·01–2·6)	0·045
70–79	74 (28)	110 (26)	1·9 (1·2–3·0)	0·007
⩾80	82 (31)	87 (20)	2·6 (1·6–4·2)	<0·001
Season				
Spring	68 (26)	69 (16)	1·0	—
Summer	71 (27)	149 (35)	0·5 (0·3–0·8)	0·001
Autumn	72 (27)	131 (30)	0·6 (0·4–0·9)	0·009
Winter	53 (20)	81 (19)	0·7 (0·4–1·1)	0·096
Concurrent condition (*vs.* all other concurrent conditions)				
No concurrent condition	14 (5)	64 (15)	0·3 (0·2–0·6)	<0·001
Concurrent condition	243 (92)	351 (82)	—	—
Malignant neoplasms	125 (47)	143 (33)	1·5 (1·1–2·1)	0·01
Lymphoid, hematopoietic, and related tissues	38 (14)	65 (15)	0·8 (0·5–1·3)	0·362
Digestive organs	19 (7)	25 (6)	1·1 (0·6–2·0)	0·75
Respiratory and intrathoracic organs	20 (8)	10 (2)	3·1 (1·4–6·6)	0·003
Breast	15 (6)	8 (2)	2·8 (1·2–6·6)	0·016
Other known†	15 (6)	23 (5)	0·9 (0·5–1·8)	0·852
Uncertain or unknown behaviour‡	18 (7)	12 (3)	2·3 (1·1–4·7)	0·029
Autoimmune diseases	32 (12)	78 (18)	0·5 (0·3–0·8)	0·005
Cardiovascular diseases	51 (19)	52 (12)	1·5 (1·0–2·3)	0·051
Respiratory diseases	15 (6)	16 (4)	1·4 (0·7–2·8)	0·384
Immunological diseases	10 (4)	12 (3)	1·2 (0·5–2·8)	0·659
Renal diseases	33 (13)	38 (9)	1·3 (0·8–2·1)	0·309
Alcoholism	16 (6)	11 (3)	2·2 (1·01–4·7)	0·047
Liver diseases	23 (9)	27 (6)	1·3 (0·7–2·2)	0·444
Diabetes	13 (5)	37 (9)	0·5 (0·3–0·9)	0·025
Post-operative status	6 (2)	12 (3)	0·7 (0·3–1·9)	0·507
Other conditions	37 (14)	63 (15)	0·8 (0·5–1·3)	0·383
Condition not described	1 (0)	1 (0)	1·5 (0·0–53·1)§	0·793
Not known/recorded	7 (3)	15 (3)		
Antibiotic therapy (*vs.* none)				
None	19 (7)	4 (1)	1·0	—
Only antibiotics with no anti-listerial activity	16 (6)	18 (4)	0·2 (0·1–0·7)	0·007
Mix	36 (14)	60 (14)	0·1 (0·0–0·4)	<0·001
Only antibiotics with anti-listerial activity	120 (45)	267 (62)	0·01 (0·0–0·3)	<0·001
Not known/recorded	73 (28)	81 (19)		
Treatment to reduce gastric acid secretion				
No	76 (29)	155 (36)	1·0	—
Yes	47 (18)	55 (13)	1·7 (1·1–2·8)	0·022
Not known/recorded	141 (53)	220 (51)		

OR, Odds ratio; CI, confidence interval.

* Mantel–Haenszel odds ratios; only categories with significant findings are presented.

† Eye, brain and other parts of the CNS; male genital organs; urinary tract; female genital organs; bone and articular cartilage; skin; thyroid and endocrine glands; lip, oral cavity or pharynx; mesothelial and soft tissues; and multiple malignancies.

‡ Ill-defined, secondary and unspecified neoplasms, or those of uncertain or unknown behaviour. The latter may not be malignant.

§ Exact confidence intervals were used.

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Table 4. *Factors independently associated with mortality in cases of* L. monocytogenes *infection, England and Wales, 2005–2009** (*n* = 694)

Variable	OR (95% CI)	*P* value
Concurrent conditions		
No concurrent condition	0·3 (0·2–0·6)	0·001
Other concurrent condition (not listed below)	1·0	—
Malignant neoplasm (Mal. neo.) of the breast	4·4 (1·7–11·3)	0·002
Mal. neo. of respiratory and intrathoracic organs	3·3 (1·4–7·5)	0·005
Mal. neo. of uncertain or unknown behaviour†	2·5 (1·1–5·6)	0·032
Alcoholism	4·0 (1·7–9·4)	0·002
Not known/recorded	0·6 (0·2–1·6)	0·342
Season		
Summer/autumn	1·0	—
Winter/spring	1·6 (1·1–2·3)	0·007
Age (yr)		
<60	1·0	—
60–69	1·6 (1·0–2·7)	0·068
70–79	2·5 (1·5–4·1)	0·001
⩾80	3·7 (2·2–6·2)	<0·001
Antibiotic therapy		
None	1·0	—
Only antibiotics with no anti-listerial activity	0·2 (0·04–0·7)	0·018
Mix	0·1 (0·04–0·4)	0·001
Only antibiotics with anti-listerial activity	0·1 (0·03–0·3)	<0·001
Not known/recorded	0·2 (0·1–0·6)	0·005

OR, Odds ratio; CI, confidence interval.

* Multvariate logistic regression.

† Ill-defined, secondary and unspecified neoplasms, or those of uncertain or unknown behaviour. The latter may be non-malignant neoplasms.

of mortality between infections involving the CNS or bacteraemia only, either were more likely to result in death than infections of other sites. The absence of a concurrent condition and presence of autoimmune disease had a protective effect in terms of mortality in these cases. Analysis of a 5-year subset of cases identified antibiotic therapy, regardless of anti-listerial activity, as a protective factor for mortality, while illness in winter or spring was associated with an increased risk of case-fatality. Although the death rate is lower since the observed increase in listeriosis cases since 2001, the overall number of deaths has increased and, therefore, so too has the overall impact of *L. monocytogenes* on food-related deaths.

Strengths and limitations

Data from laboratory surveillance of this kind are likely to disproportionately ascertain cases from the more severe end of the clinical spectrum, increasing the case-fatality rate and the prevalence of exposure of some of the factors under consideration (e.g. concurrent conditions). Our study considered a longer period and larger number of individuals than previous studies of mortality in listeriosis cases [2, 4, 15], which would have also been subject to similar reporting artefacts. The response rate to the clinical questionnaire, which captured information on mortality, and the availability of death data on these questionnaires were both high for the duration of the study and was not influenced by age or sex, therefore minimizing differential ascertainment of mortality. However, some deaths may not have been captured if the patient died after the clinical questionnaire was completed and listeriosis was not recorded on the death certificate and, therefore, not included in the weekly death notification returns from the ONS. There were few instances where a death was reported in the weekly death notification returns from the ONS but not in the clinical questionnaire and so we consider our results to be comparable to those derived from other surveillance datasets that are not supplemented with routine death notification returns.

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Unlike previous studies, we elected to use all other conditions as the reference population for each concurrent condition subgroup. This more accurately represents the population at risk of contracting and dying from *L. monocytogenes* infections and we have highlighted those concurrent conditions that impact most on mortality. However, by doing so we may have underestimated the full effect of specific concurrent conditions on mortality. In addition, by building a categorical concurrent condition variable for the multivariate analysis based on increasing disease prevalence, each case could only be assigned to a single concurrent condition code. We acknowledge that such a data-driven, exploratory approach may result in the effect of concurrent conditions with the least prevalence being masked by higher prevalence conditions for cases with more than one concurrent condition. However, this method ensures that the most prevalent concurrent condition groups associated with mortality are appropriately represented in the multivariate analysis. The alternative method would be to pre-group conditions by biological plausibility or ICD-10 coding. While such a method has a greater hypothesis-testing nature, some important conditions may be masked by other conditions of the same group with opposing effects. Missing data or 'unknown' responses were coded to ensure their inclusion, rather than exclusion, from multivariate models, and in some instances these missing exposures were associated with mortality. This is likely to be a reporting artefact because clinicians will have a less complete clinical picture for cases that die before or soon after hospital admission.

Comparison with other studies

The decreasing trend in listeriosis mortality observed in this study is supported by the findings of other studies considering similar periods [2, 16]. Three previous studies have used multivariate logistic regression analysis on cohorts of non-pregnancy-related listeriosis cases to identify prognostic factors for mortality [2, 4, 15]. An American study [2] and and a Spanish study [15] both also identified older age (described as $\geqslant 70$ years and $\geqslant 65$ years, respectively) as risk factors for mortality, while a Danish study [4] identified age as an effect modifier of the risk associated with concurrent conditions. The Danish and American studies both found non-haematological malignancies to be independently associated with mortality, which would support our findings of specific non-haematological malignancies (those of the breast and intrathoracic organs). The Danish study found that infection with a serogroup 4 isolate had an associated increased risk of mortality compared to those infected with an isolate of serogroup 1/2, while the Spanish study supported our finding of no such association. The American study did not consider serotyping in their analysis but was the only study to also consider alcoholism as a stand-alone condition and, like us, they found it to be independently associated with mortality. Furthermore, the Spanish and American groups identified steroid medications and kidney disease/renal failure as independently associated with mortality. Such findings were not reflected in our study or the Danish study.

Subset analysis 2005–2009

When compared to those who received no antibiotic therapy, receipt of any antibiotic therapy had a protective effect on mortality. There was no difference in mortality associated with cases who received empirical therapy with antibiotics with anti-listerial activity only, those who received empirical therapy with antibiotics without anti-listerial activity only or those who received both antibiotics with and without listerial activity. We have, therefore, not shown there to be a benefit of appropriate early treatment compared to delayed or inappropriate treatment with regards mortality. England and Wales experience higher levels of all-cause mortality in the winter than in the summer, with the elderly most vulnerable during this period [17]. This may contribute to the seasonality associated with listeriosis deaths as per our findings, especially given that the elderly are a high-risk group for listeriosis.

The American study investigated receipt of any antibiotics as a putative risk factor while the Spanish study compared receipt of adequate empirical treatment and combined therapy with an aminoglycoside *vs.* inadequate therapy. Neither study found an independent association with mortality although the American group found receipt of antibiotics to interact with receipt of steroid medication.

Implications

The impact of listeriosis is likely to increase in the future as an increasing life expectancy results in people living longer with concurrent conditions [18]. This supports the need for policy-makers and

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clinicians to more broadly advise those at risk of contracting and dying as a consequence of this disease, which is foodborne and therefore preventable. By combining the findings from the current study with risk and prevalence estimates from recent research in England on *Listeria* risk by concurrent condition [19], we present a risk/prevalence matrix for listeriosis that also highlights conditions that impact most on mortality (see Supplementary Table S2, available online).

We have highlighted several concurrent conditions that increase the risk of mortality in cases of listeriosis. However, it is worth noting, that the presence of any concurrent condition is also a risk factor, reinforcing the need for food safety advice for all vulnerable groups. The impact of inadequate (anything other than empirical therapy with antibiotics with anti-listerial activity) and/or late antibiotic therapy, seasonality and reduced gastric acid status on survival should be further investigated.

NOTE

Supplementary material accompanies this paper on the Journal's website (http://journals.cambridge.org/hyg).

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DECLARATION OF INTEREST

None.

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