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ORIGINAL ARTICLE

Antibiotic treatment for invasive nonpregnancy-associated listeriosis and mortality: a retrospective cohort study

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Abstract

Little evidence exists addressing the clinical value of adding gentamicin to ampicillin for invasive listeriosis. A multicenter retrospective observational study of nonpregnant adult patients with invasive listeriosis (primary bacteremia, central nervous system (CNS) disease, and others) in 11 hospitals in Israel between the years 2008 and 2014 was conducted. We evaluated the effect of penicillin-based monotherapy compared with early combination therapy with gentamicin, defined as treatment started within 48 h of culture results and continued for a minimum of 7 days. Patients who died within 48 h of the index culture were excluded. The primary outcome was 30-day all-cause mortality. A total of 190 patients with invasive listeriosis were included. Fifty-nine (30.6%) patients were treated with early combination therapy, 90 (46.6%) received monotherapy, and 44 (22.8%) received other treatments. Overall 30-day mortality was 20.5% (39/190). Factors associated with mortality included lower baseline functional status, congestive heart failure, and higher sequential organ failure assessment score. Source of infection, treatment type, and time from culture taken date to initiation of effective therapy were not associated with mortality. In multivariable analysis, monotherapy was not significantly associated with increased 30-day mortality compared with early combination therapy (OR 1.947, 95% CI 0.691–5.487). Results were similar in patients with CNS disease (OR 3.037, 95% CI 0.574–16.057) and primary bacteremia (OR 2.983, 95% CI 0.575–15.492). In our retrospective cohort, there was no statistically significant association between early combination therapy and 30-day mortality. A randomized controlled trial may be necessary to assess optimal treatment.

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Background

Invasive infection with *Listeria monocytogenes* is a serious illness characterized by up to 46% mortality [1–7]. Currently, the recommended therapy is an aminopenicillin with or without the addition of gentamicin ("combination therapy") [8]. While the choice of an aminopenicillin is supported by clinical experience of treatment success [9–11], the addition of gentamicin is based on *in vitro* studies which showed synergism between the two antibiotics [12–17]. Results of *in vivo* studies have been contradictory regarding the superiority of combination to therapy with ampicillin alone ("monotherapy") [18–21].

Due to the rarity of human listeriosis, no randomized controlled trials have been carried out evaluating efficacy of different antibiotic regimens and available data come from observational studies. Among studies addressing combination therapy and mortality [1, 22–29], many reported outcomes exclusively in patients with central nervous system (CNS) infection [22, 24, 27, 28]. The results were not consistent, with some studies indicating a lack of benefit or even harm resulting from combination therapy [22, 23, 25–29] and others finding an association with decreased mortality [1, 24]. One factor which may possibly explain some of this variation is the timing of therapy. As listeriosis is a rare entity, patients seldom receive empiric combination therapy, and gentamicin is typically added only after initial results of microbiologic testing. Delayed initiation of an aminoglycoside could decrease the utility of combination therapy and bias results towards lack of efficacy.

The incidence of listeriosis in Israel is higher than that reported by other developed countries [3, 30, 31], and the need to address the issue of optimal therapy is pressing. The objective of this study is to evaluate the efficacy of antibiotic therapy on invasive *L. monocytogenes* infections while adjusting for the timing of treatment onset.

Methods

Study design

This was a retrospective cohort study of patients who were hospitalized in eleven acute care medical centers in Israel between 1 January 2008 and 31 December 2014. The study included 10,128 (60.9%) out of the total of 16,644 admission beds in Israel [32] and included six tertiary centers and five secondary medical centers. The study was approved by the ethics committees of all participating institutions.

Participants

We included patients aged 18 years and older in whom *L. monocytogenes* was cultured from sterile sites with clinical evidence of systemic infection or CNS involvement, including meningitis or brain abscess. Pregnant women were excluded. Patients were identified by searching the records of clinical microbiology labs in the participating hospitals. Each patient was included once only; for patients with multiple episodes of infection, data were gathered for the first episode only. Patients who died within 48 h of culture-taken date (CTD) were included in the description of demographic and clinical features but excluded from the outcome analyses on the assumption that early mortality was due to factors unassociated with therapy.

Variables

The primary outcome was all-cause 30-day mortality. Secondary analyses were planned for the primary outcome in patients with primary bacteremia and CNS involvement, respectively. The exposure was antibiotic therapy with monotherapy, early combination therapy, or others. Monotherapy was defined as treatment with an antilisterial penicillin (including ampicillin, penicillin, piperacillin, amoxicillin-clavulanate, ampicillin-sulbactam, or piperacillin-tazobactam) for at least 7 consecutive days subsequent to the culture-taken date, without concomitant effective antibiotics (including aminoglycosides) for more than 3 consecutive days. Early combination therapy was defined as treatment for at least 7 consecutive days subsequent to CTD with an antilisterial beta lactam and gentamicin; the latter initiated within 48 h of culture results. Information on potential confounders was gathered including data on patient demographics, background medical conditions, sepsis severity on CTD, and antibiotic therapy prior to admission. The information was obtained retrospectively from patients' written and electronic records.

Statistical analysis

We compared patients with *L. monocytogenes* infection who received monotherapy, early combination therapy or other therapy, and a 30-day mortality. Categorical variables were compared using the χ^2 test and continuous variables using the *t* test or Mann-Whitney *U* test according to their distribution. Confounders and other risk factors for mortality found significant on univariate analysis and noncorrelated were entered into a binomial logistic regression model. To further control for the effects of confounding, a propensity score

method with stratification was used. A propensity score for receiving early combination therapy was calculated by running a logistic regression using variables which were found to be associated with combination therapy on univariate analysis. The propensity score was divided into four equally sized groups using quartiles, and a conditional logistic regression for a 30-day mortality was then performed stratifying on these quartiles. Odds ratios (ORs) with 95% confidence intervals (CIs) are reported. Analyses were conducted using IBM SPSS version 25 software.

Results

One hundred ninety-three nonpregnant adults with invasive listeriosis were identified; most patients were women (108, 56.0%) and fully functional (143, 74.1%). The median age was 69 (60–81) years. The median duration of illness prior to CTD was 2 (1–3) days, and most (162, 83.7%) patients did not receive antibiotics prior to CTD. Sixty-three (32.6%) patients had CNS involvement, 124 (64.2%) had primary bacteremia, and 6 (3.1%) had other diagnoses. Fifty-nine (30.6%) patients were treated with early combination therapy, 90 (46.6%) received monotherapy, and 44 (22.8%) received other treatments (Fig. 1). Factors associated with early combination therapy included fully functional status and CNS involvement, while factors associated with monotherapy included Arab ethnicity and primary bacteremia. Further information is available in Table 1.

A total of 190 patients were available for the univariate and multiple-variable analyses after excluding early mortality. Overall 30-day mortality was 20.5% (39/190); mortality among patients with CNS involvement was 21.0% (13/62) and 24.4% (30/123) in patients older than 65 years. Factors associated with survival included higher baseline functional capacity. Factors associated with a 30-day mortality included congestive heart failure (CHF), higher sequential organ failure assessment (SOFA) score on CTD, and elevation of liver function tests (LFTs) greater than two times the upper limit of normal on CTD (Table 2). Source of infection, treatment type, and time from CTD to initiation of appropriate therapy were not associated with mortality.

The multiple-variable analysis included all of the factors which were significantly associated with mortality except elevated LFTs which correlated with SOFA score. Additionally, the exposure variable was forced into the model. Factors associated with greater 30-day mortality in multiple-variable analysis included increasing SOFA score (OR 1.186, 95% CI 1.085–1.296) and treatment other than early combination therapy or monotherapy (OR 3.899, 95% CI 1.228–12.382) (Table 3). Fully functional status at baseline was associated with lower mortality (OR 0.343, 95% CI 0.153–0.768). Monotherapy had a nonsignificant trend to higher 30-day mortality compared with early combination therapy (OR 1.947, 95%CI 0.691–5.487). After stratifying by the propensity score, increasing SOFA score (OR 1.136, 95% CI 1.075–1.201) and treatment other than early combination therapy or monotherapy (OR 3.930, 95% CI 1.407–10.977) remained associated with mortality (Table 4). The trend toward higher mortality with monotherapy compared with early combination therapy remained nonsignificant (OR 2.312, 95% CI 0.915–5.843). Results were similar in separate analyses of patients with primary bacteremia and CNS involvement (Supplementary materials). Length of beta lactam-aminoglycoside treatment was not independently associated with mortality when included in the regression (OR 0.666 for > 3 days vs. 0, 95% CI 0.140–3.161).

Discussion

In a retrospective cohort of patients with invasive listeriosis, overall 30-day mortality was 20.5%. No difference was observed in mortality between patients who received a penicillin-based monotherapy or combination therapy with gentamicin initiated within 48 h of culture result after adjusting for other mortality risk factors. Treatment other than penicillin-based monotherapy or early penicillin-aminoglycoside combination therapy was associated with higher mortality.

The use of beta lactam-aminoglycoside combination therapy for infections based on in vitro evidence of synergy has come into question in recent years [33–37]. In light of these data, there has been a reevaluation of the efficacy of combination therapy in patients with listeriosis. More recent in vitro data has shown that the addition of gentamicin can lead to persistence of intracellular infection and promote bacterial survival [38]. Research on pregnancy-associated disease indicates that gentamicin may increase dissemination of listeria from the placenta to other organs [39]. Clinical data from several retrospective cohort studies [22, 23, 25–28] also failed to support the addition of an aminoglycoside and in some cases indicated increased mortality with combination therapy. However, small sample size and a lack of adjustment to confounders limit the generalizability of their results.

The largest study to date on invasive listeriosis (MONALISA) evaluated a prospective cohort of 818 patients for a 3-month mortality [1]. They found that treatment with gentamicin was associated with lower mortality among patients with CNS involvement or non-CNS, nonmaternal-fetal bacteremia (OR 0.60, 95% CI 0.38–0.94), and that amoxicillin-gentamicin combination therapy given for greater than three days was independently associated with lower mortality compared with monotherapy (OR 0.35, 95% CI 0.22–0.56). However, the adjusted analysis did not include bacteremia/CNS infection as a variable although this was an

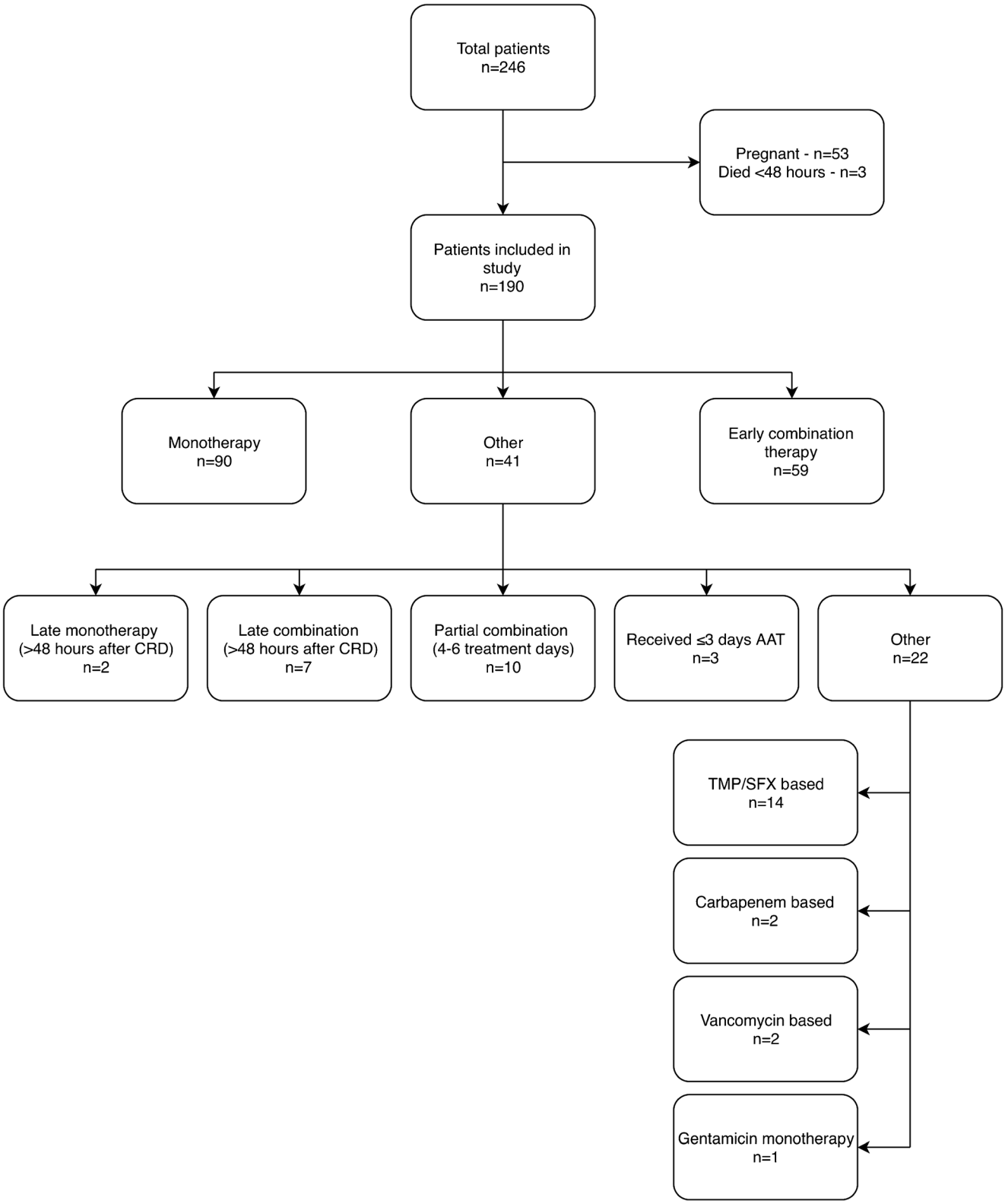

Fig. 1 Patient flow diagram. AAT—appropriate antibiotic therapy; CRD—culture result date; TMP/SFX—trimethoprim/sulfamethoxazole

important confounder in the cohort (as in ours) given that significantly more patients with CNS infection received combination therapy (192/252 vs. 170/427, $p < 0.001$) while experiencing a lower rate of a 3-month mortality (72/252 vs. 194/427, $p < 0.001$). This raises the possibility that part of the advantage observed with combination therapy was due

Table 1 Factors associated with treatment

Variable	Early combination ($n = 59$)	Monotherapy ($n = 90$)	Other ($n = 44$)	p (early combi vs. mono)	p (early combi vs. other)
Age, median (IQR)	69 (61–78)	72 (59–83)	72 (60–83)	0.073	0.106
Male	27 (45.8%)	33 (36.7%)	25 (56.8%)	0.268	0.267
Ethnicity				0.024	0.096
Jewish	55 (93.5%)	75 (83.3%)	38 (86.4%)		
Arab	1 (1.7%)	13 (14.4%)	5 (11.4%)		
Other	3 (5.1%)	2 (2.2%)	1 (2.3%)		
Hospital				0.312	0.638
Region				0.103	0.460
North	8 (13.6%)	7 (7.8%)	6 (13.6%)		
Center	40 (67.8%)	50 (55.6%)	24 (54.5%)		
East	9 (15.3%)	29 (32.2%)	12 (27.3%)		
South	2 (3.4%)	4 (4.4%)	2 (4.5%)		
Functional capacity				0.043	0.445
Independent	50 (84.7%)	60 (66.7%)	33 (75.0%)		
Partially dependent	6 (10.2%)	23 (25.6%)	8 (18.2%)		
Fully dependent	3 (5.1%)	7 (7.8%)	3 (6.8%)		
Chronic kidney disease				0.710	0.413
None	49 (83.1%)	70 (77.8%)	39 (88.6%)		
Stages I–II	7 (11.9%)	13 (14.4%)	2 (4.5%)		
Stages III–V	3 (5.1%)	7 (7.8%)	3 (6.8%)		
Malignancy				0.194	0.152
No malignancy	22 (37.3%)	47 (52.2%)	24 (54.5%)		
Solid tumor	23 (39.0%)	28 (31.1%)	10 (22.7%)		
Hematologic	14 (23.7%)	15 (16.7%)	10 (22.7%)		
Chemotherapy	20 (33.9%)	31 (34.4%)	13 (29.5%)	0.945	0.640
HIV	0	0	0		
Steroids	27 (45.8%)	29 (32.2%)	12 (27.3%)	0.095	0.056
Other immunosuppressive medications	9 (15.3%)	20 (22.2%)	4 (9.1%)	0.293	0.389
Sold organ transplant	0	1 (1.1%)	0	1.000	
Stem cell transplant	6 (10.2%)	3 (3.3%)	0	0.156	0.036
Diabetes	17 (28.8%)	24 (26.7%)	6 (13.6%)	0.774	0.067
CHF	5 (8.5%)	15 (16.7%)	8 (18.2%)	0.151	0.142
IHD	13 (22.0%)	16 (17.8%)	8 (18.2%)	0.521	0.631
Alcoholism	0	0	0		
Hemiplegia	2 (3.4%)	2 (2.2%)	0	0.649	0.506
Dementia	2 (3.4%)	4 (4.4%)	1 (2.3%)	1.000	1.000
Pulmonary disease	7 (11.9%)	9 (10.0%)	2 (4.5%)	0.719	0.294
Connective tissue disease	6 (10.2%)	7 (7.8%)	3 (6.8%)	0.613	0.729
Liver disease	4 (6.8%)	10 (11.1%)	4 (9.1%)	0.567	0.721
PVD	1 (1.7%)	6 (6.7%)	2 (4.5%)	0.245	0.574
CVD	2 (3.4%)	3 (3.3%)	4 (9.1%)	1.000	0.398
PUD	3 (5.1%)	6 (6.7%)	3 (6.8%)	1.000	1.000
SOFA score on CTD, median (IQR)	4 (2–8)	4 (2–8)	4 (1–8)	0.987	0.660
LFT > 2*UL on CTD	10 (16.9%)	25 (27.8%)	7 (15.9%)	0.127	0.888
Diagnosis				< 0.001	0.265
Primary BSI	27 (45.8%)	70 (77.8%)	27 (61.4%)		
CNS involvement	31 (52.5%)	16 (17.8%)	16 (36.4%)		
Other	1 (1.7%)	4 (4.4%)	1 (2.3%)		
AB prior to CTD	11 (18.6%)	14 (15.6%)	6 (13.6%)	0.622	0.498
Length of symptoms prior to CTD (days), median (IQR)	1 (0–3)	2 (0–4)	2 (1–3)	0.343	0.114
Time from CTD to AAT (days), median (IQR)	3 (1–4)	3 (1–4)	3 (1–5)	0.061	0.052

AAT appropriate antibiotic therapy, *AB* antibiotic, *BSI* bloodstream infection, *CHF* congestive heart failure, *CNS* central nervous system, *CTD* culture-taken date, *CVD* cerebrovascular disease, *HIV* human immunodeficiency virus, *IHD* ischemic heart disease, *IQR* intraquartile range, *LFT* liver function tests, *PAD* pregnancy-associated disease, *PUD* peptic ulcer disease, *PVD* peripheral vascular disease, *SOFA* sequential organ failure assessment, *2*UL* 2× the upper limit of normal

Table 2 Univariate analysis, 30-day mortality

Variable	Alive ($n = 151$)	Dead ($n = 39$)	p
Age, median (IQR)	69 (59–81)	72 (65–83)	0.086
Male	83 (55.0%)	25 (64.1%)	0.304
Ethnicity			0.449
Jewish	130 (86.1%)	35 (89.7%)	
Arab	15 (9.9%)	4 (10.3%)	
Other	6 (4.0%)	0	
Hospital			0.548
Region			0.456
North	19 (12.6%)	2 (5.1%)	
Center	89 (58.9%)	22 (56.4%)	
East	37 (24.5%)	13 (33.3%)	
South	6 (4.0%)	2 (5.1%)	
Functional capacity			0.003
Independent	120 (79.5%)	21 (53.8%)	
Partially dependent	24 (15.9%)	12 (30.8%)	
Fully dependent	7 (4.6%)	6 (15.4%)	
Chronic kidney disease			0.172
None	126 (83.4%)	30 (76.9%)	
Stages I–II	18 (11.9%)	4 (10.3%)	
Stages III–V	7 (4.6%)	5 (12.8%)	
Malignancy			0.875
No malignancy	72 (47.7%)	20 (51.3%)	
Solid tumor	49 (32.5%)	11 (28.2%)	
Hematologic	30 (19.9%)	8 (20.5%)	
Chemotherapy	49 (32.5%)	15 (38.5%)	0.479
HIV	0	0	
Steroids	55 (36.4%)	13 (33.3%)	0.720
Other immunosuppressive medications	28 (18.5%)	5 (12.8%)	0.400
Sold organ transplant	1 (0.7%)	0	1.000
Stem cell transplant	9 (6.0%)	0	0.208
Diabetes	39 (25.8%)	8 (20.5%)	0.493
CHF	18 (11.9%)	10 (25.6%)	0.031
IHD	27 (17.9%)	8 (20.5%)	0.705
Alcoholism	0	0	
Hemiplegia	3 (2.0%)	1 (2.6%)	1.000
Dementia	5 (3.3%)	2 (5.1%)	0.634
Pulmonary disease	15 (9.9%)	3 (7.7%)	1.000
Connect tissue disease	13 (8.6%)	3 (7.7%)	1.000
Liver disease	14 (9.3%)	4 (10.3%)	0.767
PVD	7 (4.6%)	2 (5.1%)	1.000
CVD	7 (4.6%)	2 (5.1%)	1.000
PUD	9 (6.0%)	3 (7.7%)	0.714
SOFA score on CTD, median (IQR)	4 (0–6)	6 (4–8)	< 0.001
LFT > 2*UL on CTD	27 (17.9%)	14 (35.9%)	0.015
Treatment			0.091
Early combination	52 (34.4%)	7 (17.9%)	
Monotherapy	70 (46.4%)	20 (51.3%)	
Other	29 (19.2%)	12 (30.8%)	
Trimethoprim/sulfamethoxazole treatment (≥ 3 days)	27 (17.9%)	8 (20.5%)	0.705
Diagnosis			0.969
Primary bacteremia	97 (64.2%)	25 (64.1%)	
CNS involvement	49 (32.5%)	13 (33.3%)	
Other	5 (3.3%)	1 (2.6%)	
AB prior to CTD	24 (15.9%)	7 (17.9%)	0.757
Length of symptoms prior to CTD (days), median (IQR)	2 (0–4)	1 (1–3)	0.478
Time from CTD to AAT (days), median (IQR)	3 (1–4)	3 (1–4)	0.712

AAT appropriate antibiotic therapy, *AB* antibiotic, *BSI* bloodstream infection, *CHF* congestive heart failure, *CNS* central nervous system, *CTD* culture-taken date, *CVD* cerebrovascular disease, *HIV* human immunodeficiency virus, *IHD* ischemic heart disease, *IQR* intraquartile range, *LFT* liver function tests, *PUD* peptic ulcer disease, *PVD* peripheral vascular disease, *SOFA* sequential organ failure assessment, *2*UL* 2× the upper limit of normal

Table 3 Binomial regression

Variable	OR	95% CI lower	95% CI upper	*p*
Fully functional	0.343	0.153	0.768	0.009
CHF	1.700	0.620	4.660	0.302
SOFA score	1.186	1.085	1.296	< 0.001
Early combination				Reference
Monotherapy	1.947	0.691	5.487	0.208
Other	3.899	1.228	12.382	0.021

CHF congestive heart failure, *CI* confidence interval, *OR* odds ratio, *SOFA* sequential organ failure assessment

to confounding by clinical presentation. In addition, no information was presented on timing of appropriate therapy vis-à-vis symptom onset or diagnosis. In our cohort, no association was seen between time from symptom onset to presentation or time from CTD to onset of appropriate therapy and mortality; of the other studies published to date, two found an association between mortality and appropriate empiric therapy/time to appropriate therapy and two did not [23, 26–28]. Thus, questions remain about the role of aminoglycosides in the treatment of listeriosis, especially when there is a delay in initiation.

The 30-day mortality (20.5%) observed in our study was lower than that seen in MONALISA for bacteremic patients but similar to rates from previous retrospective studies [22–28], including a meta-analysis [2]. One reason for the differences might be variability in patient populations. The strongest predictors of mortality in our analysis were SOFA score at onset and baseline functional status; no sepsis severity scores were available for patients in the MONALISA trial, and functional status was not reported, making a comparison difficult. Additionally, differences in healthcare infrastructure may have played a role. Six of the hospitals included in our study were tertiary-level and the remaining five were secondary, with no community-level centers; all hospitals involved were university-affiliated. Notably, there was no significant difference in length of symptoms prior to diagnosis between our study and the MONALISA trial, implying that the lower mortality which we observed was not due to survival bias.

Table 4 Conditional regression stratified by propensity score

Variable	OR	95% CI lower	95% CI upper	*p*
Fully functional	0.415	0.107	1.601	0.201
CHF	1.181	0.511	2.732	0.697
SOFA score	1.136	1.075	1.201	< 0.001
Early combination				Reference
Monotherapy	2.312	0.915	5.843	0.076
Other	3.930	1.407	10.977	0.009

CHF congestive heart failure, *CI* confidence interval, *OR* odds ratio, *SOFA* sequential organ failure assessment

Our analysis had a number of limitations. First, although multicenter and inclusive of most hospital beds nationwide, the cohort size was relatively small and did not cover the entire country (11/28 hospitals nationwide). The MONALISA study that found an advantage to combination therapy included more than 800 patients with a mortality difference of 17% at 3 months; using the mortality rate we observed and assuming the odds ratio for the 30-day mortality we calculated is true, a sample size of 408 would be necessary to demonstrate significance of $\alpha = 0.05$. Second, this was a retrospective observational study and it is likely that potential confounders for choice of antibiotic treatment were not accounted for in our analysis. Third, in our definitions of antilisterial beta lactams, we included penicillin, ampicillin/amoxicillin, and piperacillin, assuming equal effectiveness. While evidence exists for the equivalence of penicillin and ampicillin [40], data comparing ampicillin with piperacillin are scarce. The mean inhibitory concentration (MIC) against *L. monocytogenes* is higher for piperacillin than ampicillin [41, 42]; however, the clinical significance of this fact is uncertain; in the only study to compare piperacillin with other antilisterial penicillins, only five patients received piperacillin as definitive therapy of whom three survived [26]. Given the widespread use of piperacillin-tazobactam as empiric therapy for sepsis in immunosuppressed patients, further investigation of its clinical efficacy in listeriosis is advisable.

In conclusion, we did not find an association between combination therapy and the 30-day mortality, although associations tended in favor of combination therapy. The optimal regimen for treatment of listeriosis remains unclear. Current global interconnectivity might allow for multicenter investigator-initiated studies of rare infections; the role of combination therapy will be best assessed in randomized controlled trials.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study was approved by the ethics committees of all participating institutions.

Informed consent Informed consent was not applicable given the retrospective observational nature of the study.

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