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Antimicrobial Activities against 84 *Listeria monocytogenes* Isolates from Patients with Systemic Listeriosis at a Comprehensive Cancer Center (1955–1997)

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Listeriosis is a serious complication in patients undergoing treatment for cancer. We present antimicrobial susceptibility profiles of 84 clinical *Listeria monocytogenes* isolates. During 1955 to 1997, in vitro susceptibility for penicillin (97.6%), ampicillin (90.7%), erythromycin (98.8%), tetracycline (96.9%), and gentamicin (98.0%) remained unchanged. All isolates were susceptible to amikacin, ciprofloxacin, imipenem, rifampin, trimethoprim-sulfamethoxazole (TMP-SMX), and vancomycin. High prevalence of clindamycin resistance (96.2%) was unexpected. Ampicillin plus gentamicin is standard therapy for systemic listerosis, and TMP-SMX may be used for patients with beta-lactam intolerance. In vitro susceptibility profiles for carbapenem and fluoronated quinolone are promising, although clinical validation is critically needed before routine use is advocated, especially for listeric patients with severe cellular immune defects.

Systemic listerosis is an infrequent opportunistic complication in patients undergoing treatment for hematologic malignancies (11, 20) or allogeneic hematopoietic stem cell transplantation (21). *Listeria monocytogenes* frequently invades the central nervous system via hematogenous dissemination, leading to meningioencephalitis, cerebritis, and/or brain abscesses (10). Response to antibiotic therapy is often good, even for patients with severe immune dysfunction (20, 21). Several antimicrobial agents exhibit in vitro activity against *L. monocytogenes* (1, 8, 13), although ampicillin-based regimens are considered the gold standard for the treatment of systemic listeric infections; aminoglycosides are often added for antimicrobial synergy (15).

Antimicrobial resistance has undergone near-exponential increase during the past decades. The use of common broad-spectrum antibiotics to treat most pathogenic bacteria, given either prophylactically or by empiric-preemptive therapy in high-risk settings, has further accentuated this trend, especially in patients with underlying malignancy. This retrospective analysis was performed to evaluate the prevalence of antimicrobial resistance in disease-related *L. monocytogenes*, isolated from patients receiving care at a comprehensive cancer center during 1955 to 1997.

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Study design. This retrospective study was performed at three intervals: 1955 to 1966 (reported in reference 11); 1970 to 1979, and 1991 to 1997. Eighty-four *L. monocytogenes* isolates were obtained from patients' blood and cerebrospinal fluid samples at the Memorial Sloan-Kettering Cancer Center in New York, N.Y. All specimens were initially processed at the Memorial Sloan-Kettering Cancer Center Microbiology Laboratory, and they also identified *L. monocytogenes* isolates and conducted antimicrobial susceptibility. *L. monocytogenes* reidentification and serotype analysis (data not shown) were undertaken at the Centers for Disease Control and Prevention, Atlanta, Ga.

Microorganism identification. *L. monocytogenes* organisms were isolated and identified by standard methods described elsewhere (11, 21).

Antimicrobial susceptibility. The antimicrobial susceptibility for 60 strains from 1955 to 1979 was performed by an agar plate antibiotic disk diffusion method (Kirby-Bauer technique) (11, 16). Fresh beef heart broth was used to supplement broth culture medium (11). The diameter (in millimeters) of each zone around the antibiotic disk was measured and interpreted according to the National Committee for Clinical Laboratory Standards (NCCLS) recommendations (16). Broth microdilution susceptibility studies were performed during 1991 to 1997. The lowest concentration of drug that inhibited the bacterial growth after incubation for 24 h was considered the MIC, and interpretive breakpoints were determined according to NCCLS guidelines (13). All antimicrobial agents were obtained from their respective manufacturers.

Of 84 *L. monocytogenes* isolates, 43 (51.2%) were isolated from cerebrospinal fluid samples, 39 (46.4%) were from blood culture specimens, and 2 (2.4%) were from patients who had extracranial end-organ infection (listeric empyema and uveitis). The overall antimicrobial in vitro susceptibility is shown in Table 1. Resistance to ampicillin (9.2%), erythromycin (1.9%), gentamicin (2%), penicillin (2.3%), tetracycline (3%), and ticarcillin-calvulanate (3.8%) was low. All isolates were susceptible to amikacin, cefazolin, cephalothin, rifampin, trimethoprim-sulfamethoxazole (TMP-SMX), and vancomycin. Eighty-seven percent showed in vitro susceptibility to chloramphenicol. High-frequency resistance to clindamycin (96.2%)

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TABLE 1. Susceptibility of *L. monocytogenesis* isolates collected from 1955 to 1997[a]

Antimicrobial agent	No. of isolates	No. (%) of susceptible strains	No. (%) of nonsusceptible strains
Penicillin	84	82 (97.6)	2 (2.3)
Ampicillin	65	59 (90.7)	6 (9.2)
Oxacillin	47	31 (55.9)	16 (34)
Methicillin	29	19 (65.5)	10 (34.4)
Timentin	26	25 (96.2)	1 (3.8)
Cefazolin	21	21 (100)	0
Cephalothin	67	67 (100)	0
Cefuroxime	26	5 (19.2)	21 (80.8)
Cefotaxime	21	7 (33.3)	14 (66.6)
Ceftriaxone	21	5 (23.8)	16 (76.1)
Clindamycin	26	1 (3.8)	25 (96.2)
Erythromycin	84	83 (98.8)	1 (1.9)
Tetracycline	66	64 (96.9)	2 (3)
Chloramphenicol	54	47 (87)	7 (12.9)
Gentamicin	52	51 (98)	1 (2)
Amikacin	23	23 (100)	0
Streptomycin	18	12 (66.6)	6 (33.3)
Kanamycin	35	34 (97.1)	1 (2.8)
Rifampin	21	21 (100)	0
Nitrofurantoin	21	10 (47.6)	11 (52.3)
TMP-SMX	26	26 (100)	0
Vancomycin	26	26 (100)	0
Ciprofloxacin	21	21 (100)	0
Norfloxacin	21	19 (90.4)	2 (9.5)
Imipenem	21	21 (100)	0

[a] Timentin, ticarcillin-clavulanate. Antimicrobial susceptibility breakpoints during 1955 to 1979 were determined by the agar plate drug diffusion method; MIC breakpoints for agar plate drug diffusion are described elsewhere (13). Microdilution technique was used to determined antimicrobial susceptibility during 1991 to 1997. Nonsusceptible strains included intermediate and resistant *L. monocytogenes* isolates.

and the broad-spectrum cephalosporins cefuroxime (80.8%), cefotaxime (66.6%), and ceftriaxone (76.1%) was also observed.

During 01 January 1991 to 31 December 1997, MICs (determined for the MICs at which both 50 and 90% of the isolates tested were inhibited) were determined by broth microdilution technique, and results are given in Table 2. The 90% inhibitory MIC for amikacin (≤16.0 μg/ml), ampicillin (1.0 μg/ml), erythromycin (≤0.25 μg/ml), gentamicin (≤1.0 μg/ml), penicillin (0.5 μg/ml), tetracycline (<0.25 μg/ml), and TMP-SMX (≤2.0 μg/ml for TMP and 38.0 μg/ml for SMX) remained within susceptible ranges. Ninetieth percentile of *L. monocytogenes* isolates showed an imipenem and ciprofloxacin MIC of ≤1.0 μg/ml.

TABLE 2. *L. monocytogenes* susceptibility profile during 1991 to 1997[a]

Antimicrobial agent	No. of isolates	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)
Penicillin	24	0.25	0.5
Ampicillin	24	0.25	1
Oxacillin	24	2	≥4.0
Timentin	24	≤1.0	4
Cefazolin	21	≤2.0	≤2.0
Cephalothin	24	≤2.0	≤2.0
Cefuroxime	24	≥32.0	≥32.0
Cefotaxime	21	16	≥64.0
Ceftriaxone	21	32	≥64.0
Clindamycin	24	≥4.0	≥4.0
Erythromycin	24	≤0.25	≤0.25
Tetracycline	24	≤2.0	≤2.0
Chloramphenicol	24	≤4.0	8
Gentamicin	24	≤1.0	≤1.0
Amikacin	24	≤16.0	≤16.0
Rifampin	21	≤1.0	≤1.0
Nitrofurantoin	21	64	≥64.0
TMP-SMX	24	≤2 and 38	≤2 and 38
Vancomycin	24	≤2.0	≤2.0
Ciprofloxacin	21	≤1.0	≤1.0
Imipenem	21	≤1.0	≤1.0

[a] Timentin, ticarcillin-clavanulate. MIC_{50} and MIC_{90}, MIC at which 50 and 90%, respectively, of the isolates tested are inhibited.

L. monocytogenes remains susceptible to a wide variety of antimicrobial agents, although as noted in this report, in vitro resistance to broad-spectrum cephalosporin antibiotics has been observed consistently (8, 13). Since the 1980s, multidrug-resistant enterococci have increased significantly both in the hospital and community environment (6, 18). Plasmids carrying genetic determinants of antibiotic resistance can successfully transfer genetic code from *Enterococcus faecalis* to *L. monocytogenes* (2, 4, 19); this observation had raised serious concerns regarding emergence of antibiotic resistance and choice of optimal initial therapy for severe listeric infections in compromised individuals. Similar to this report, others have described no significant rise in drug-resistant *L. monocytogenes* (Table 3) (5, 9, 11, 13, 22, 23). This may in part be due to the fact that most systemic listerosis is acquired from non-nosocomial environment pools, and hospital-acquired de novo invasive listerosis even in patients with severe immune deficiency is rare (10).

Penicillin and ampicillin are bactericidal against most strains of *L. monocytogenes*; however, in the preferred intracellular milieu, these microorganisms become more recalcitrant and

TABLE 3. Interval antimicrobial resistance profile of clinical *L. monocytogenes* isolates[a]

Antimicrobial agent	No. (%) of isolates susceptible or resistant during					
	1955–1966		1970–1979		1991–1997	
	Susceptible	Resistant	Susceptible	Resistant	Susceptible	Resistant
Penicillin	17 (94.4)	1 (5.6)	39 (97.5)	1 (2.5)	24 (100)	0
Ampicillin	4 (100)	0	29 (82.9)	6 (17.1)	24 (100)	0
Erythromycin	17 (94.4)	1 (5.6)	41 (100)	0	24 (100)	0
Tetracycline	16 (88.9)	2 (11.1)	22 (100)	0	24 (100)	0
Chloramphenicol	14 (77.8)	4 (22.2)	9 (90)	1 (10)	22 (91.7)	2 (8.3)

[a] During 1955 to 1979 a disc susceptibility test was used (11, 16), and during 1990 to 1997 a microdilution method was employed (13).

even highly effective drugs are rendered bacteriostatic at best (7, 9, 15). The lack of in vivo bactericidal antilisteric effect becomes important in the treatment of systemic opportunistic infections in patients with compromised adaptive cellular immunity (10, 20). Therefore, various drug combinations were explored to evaluate in vivo enhancement of antilisteric activity. Animal studies demonstrated 100-fold greater killing of *L. monocytogenes* following therapy with penicillin or ampicillin plus gentamicin (12, 15). Presently, combination antimicrobials are considered standard for treatment of opportunistic systemic listerosis (10, 11, 15, 21). However, this bactericidal synergism has not been observed for trimethoprim-sulfamethoxazole plus aminoglycoside, amoxicillin, or ciprofloxacin (1). In fact, indiscriminate use of drug combinations, such as ciprofloxacin plus rifampin, may result in antibacterial antagonism and may increase chances of treatment failure (1).

The new fluorinated quinolones, such as levofloxacin, sparfloxacin, gemifloxacin, and moxifloxacin, are bactericidal against *L. monocytogenes*. These antimicrobials can achieve greater than 99.9% bacterial killing with no evidence of bacterial regrowth (3, 7, 13, 14). However, no measurable antilisteric effect of ciprofloxacin in intracellular cell culture experiments (17) cautions against therapeutic intervention. Clinical validation is critically needed to determine the role of new-generation fluorinated quinolones and carbapenems in the treatment of *L. monocytogenes* infections in patients at risk.

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REFERENCES

1. **Boisivon, A., C. Guiomar, and C. Carbon.** 1990. In vitro bactericidal activity of amoxicillin, gentamicin, rifampicin, ciprofloxacin and trimethoprim-sulfamethoxazole alone or in combination against Listeria monocytogenes. Eur. J. Clin. Microbiol. Infect. Dis. **9:**206–209.
2. **Charpentier, E., G. Gerbaud, C. Jacquet, J. Rocourt, and P. Courvalin.** 1995. Incidence of antibiotic resistance in *Listeria* species. J. Infect. Dis. **172:**277–281.
3. **Cherubin, C. E., and C. W. Stratton.** 1994. Assessment of the bactericidal activity of sparfloxacin, ofloxacin, levofloxacin, and other fluoroquinolones compared with selected agents of proven efficacy against *Listeria monocytogenes*. Diagn. Microbiol. Infect. Dis. **20:**21–25.
4. **Doucet-Populaire, F., P. Trieu-Cuot, I. Dosbaa, A. Andremont, and P. Courvalin.** 1991. Inducible transfer of conjugative transposons Tn*1545* from *Enterococcus faecalis* to *Listeria monocytogenes* in the digestive tracts of gnotobiotic mice. Antimicrob. Agents Chemother. **35:**185–187.
5. **Espaze, E. P., and A. E. Reynaud.** 1988. Antibiotic susceptibility of Listeria: in vitro studies. Infection **16:**160–164.
6. **Gold, H. S., and R. C. Moellering, Jr.** 1996. Antimicrobial-drug resistance. N. Engl. J. Med. **335:**1445–1453.
7. **Heger, W., M. P. Dierich, and F. Allerberger.** 1997. In vitro susceptibility of *Listeria monocytogenes*: comparison of the E test with the agar dilution test. Chemotherapy **43:**303–310.
8. **Hof, H., T. Nichterlein, and M. Kretschmar.** 1997. Management of listeriosis. Clin. Microbiol. Rev. **10:**345–357.
9. **Jones, E. M., and A. P. MacGowan.** 1995. Antimicrobial chemotherapy of human infection due to *Listeria monocytogenes*. Eur. J. Clin. Microbiol. Infect. Dis. **14:**165–175.
10. **Lorber, B.** 1997. Listerosis. Clin. Infect. Dis. **24:**1–11.
11. **Louria, D. B., T. Hensle, D. Armstrong, H. S. Collins, A. Blevins, D. Krugman, and M. Buse.** 1967. Listeriosis complicating malignant disease: a new association. Ann. Intern. Med. **67:**261–281.
12. **MacGowan, A., M. Wooton, K. Bowker, H. A. Holt, and D. Reeves.** 1998. Ampicillin-aminoglycoside interaction studies using *Listeria monocytogenes*. J. Antimicrob. Chemother. **41:**417–418.
13. **Marco, F., M. Almela, J. Nolla-Salas, P. Coll, I. Gasser, M. D. Ferrer, M. de Simon, and the Collaborative Study Group of Listeriosis of Barcelona.** 2000. In vitro activity of 22 antimicrobial agents against *Listeria monocytogenes* strains isolated in Barcelona, Spain. Diagn. Microbiol. Infect. Dis. **38:**259–261.
14. **Michelet, C., J. L. Avril, C. Arvieux, C. Jacquelinet, N. Vu, and F. Cartier.** 1997. Comparative activity of new fluoroquinolones, alone or in combination with amoxicillin, trimethoprim-sulfamethoxazole, or rifampin, against intracellular *Listeria monocytogenes*. Antimicrob. Agents Chemother. **41:**60–65.
15. **Moellering, R. C., Jr., G. Medoff, I. Leech, C. Wennersten, and L. J. Kunz.** 1972. Antibiotic synergism against *Listeria monocytogenes.* Antimicrob. Agents Chemother. **1:**30–34.
16. **National Committee for Clinical Laboratory Standards.** 1997. Performance standards for antimicrobial disk susceptibility tests, 6th ed. Approved standard. Document M2-A6. National Committee for Clinical Laboratory Standards, Wayne, Pa.
17. **Nichterlein, T., and H. Hof.** 1991. Effect of various antibiotics on *Listeria monocytogenes* multiplying in L 929 cells. Infection **19:**234–238.
18. **Ostrowsky, B. E., W. E. Trick, A. H. Sohn, S. B. Quirk, S. Holt, L. A. Carson, B. C. Hill, M. J. Arduino, M. J. Kuehnert, and W. R. Jarvis.** 2001. Control of vancomycin-resistant enterococcus in health care facilities in a region. N. Engl. J. Med. **344:**1427–1433.
19. **Poyart-Salmeron, C., C. Carlier, P. Trieu-Cuot, A. L. Courtieu, and P. Courvalin.** 1990. Transferable plasmid-mediated antibiotic resistance in *Listeria monocytogenes*. Lancet **335:**1422–1426.
20. **Safdar, A., and D. Armstrong.** 2001. Infectious morbidity in critically ill patients with cancer. Crit. Care Clin. **17:**531–570.
21. **Safdar, A., E. B. Papadopoulous, and D. Armstrong.** 2002. Listerosis in recipients of allogeneic blood and marrow transplantation: thirteen-year review of disease characteristics, treatment outcomes, and a new association with human cytomegalovirus infection. Bone Marrow Transplant. **29:**913–916.
22. **Seeliger, H. P. R.** 1961. Listerosis. Hafner Publishing Co., Inc., New York, N.Y.
23. **Winslow, D. L., and G. A. Pankey.** 1982. In vitro activity of trimethoprim and sulfamethoxazole against *Listeria monocytogenes*. Antimicrob. Agents Chemother. **22:**1000–1004.