Original Report

Bacteremias caused by *Escherichia coli* in cancer patients – analysis of 65 episodes

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Objectives: The aims of this study were to evaluate risk factors, clinical presentation, outcome and antimicrobial susceptibility in patients with *Escherichia coli* bacteremia occurring over seven years in a single cancer hospital.

Methods: Sixty five episodes of bacteremia from *E. coli* appearing over seven years from 12,301 admissions in a single cancer institution were retrospectively analyzed.

Results: The proportion of bacteremia caused by *E. coli* among Gram-negative bacteremia was 20.8% (the second most common organism after *Pseudomonas aeruginosa*), and infection-associated mortality was 17%. The incidence in 1989–1995 varied from 14.3 to 24.7%. The most common risk factors were: solid tumors as the underlying disease (70.7%); central venous catheter insertion (32.3%); prior surgery (46.2%), and prior chemotherapy within 48 h (44.4%). Neutropenia and urinary catheters did not place patients at high risk in any of the subgroups. When we compared the two subgroups of 61 cases of bacteremia – monomicrobial and polymicrobial (when *E. coli* was isolated from blood culture with another microorganism) – we found that acute leukemia and breakthrough (recurrence while receiving antibiotics) bacteremia were more frequently associated with polymicrobial *E. coli* bacteremia. There was also a difference in infection-associated mortality: monomicrobial bacteremia due to *E. coli* only had a significantly lower mortality in comparison with polymicrobial *E. coli* bacteremia (8.9 vs 35.0%, respectively; $P<0.03$).

Conclusion: The susceptibility of 115 *E. coli* strains isolated from 65 episodes of bacteremia was stable. Only two episodes caused by quinolone-resistant strains occurred, both in 1995, after six years of using ofloxacin for prophylaxis in neutropenic patients in our hospital. We found that 85.2–91.3% of all strains were susceptible to aminoglycosides, 97.8% to quinolones, and 90–100% to third generation cephalosporins and imipenems. The patients most commonly infected had solid tumors and the mortality was only 17%.

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Enterobacteriaceae are some of the most common sources of nosocomial bloodstream infections and were the second most common group of organisms (following staphylococci) isolated from blood cultures in large epidemiologic studies in cancer patients.[1,2]

Escherichia coli isolated from blood cultures is generally susceptible to quinolones and third-generation cephalosporins; however, quinolone-resistant *E. coli* was reported in cancer centers using quinolones for infection prevention during neutropenia.[3,4] Quinolone resistance in *E. coli* is still uncommon and appears in 1–2% of all isolates from blood cultures in cancer centers using quinolones either for prophylaxis or empiric therapy.[5,6] Resistance to third-generation cephalosporins and aminoglycosides by *E. coli* is steadily increasing and appears sometimes during initial (empiric) therapy.[7] Resistance to imipenem is exceptional. Mortality from *E. coli* bacteremia in cancer patients is reported to be 15–25%, and *E. coli* can cause septic shock with a fatal outcome. The mortality from *E. coli* bacteremia is higher than that from *Acinetobacter* spp., *Stenotrophomonas maltophilia*, or staphylococcal bacteremias.[2,8]

The aim of this investigation was to study incidence, epidemiology, risk factors, outcome and resistance to antimicrobials in cancer patients with bacteremia from *E. coli* within the last seven years in a single cancer hospital where quinolones have been used for prophylaxis since 1990.

PATIENTS AND METHODS

Patients

We have observed 506 cases of gram-negative rod bacteremias among 869 bacteremic episodes from January 1, 1989 until December 31, 1995, and 65 were due to *E. coli*. One hundred and fifteen strains of *E. coli*

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were identified from 61 episodes. From patients charts we recorded: age, sex, underlying disease, central venous catheter, neutropenia <500/mL, colonization with *E. coli* of another body site, prior surgery, endoscopy (within seven days), prior chemotherapy, polymicrobial or monomicrobial cultures, prior prophylaxis with quinolones, prior therapy with third-generation cephalosporins and aminoglycosides, and susceptibility of isolated strains. Clinical symptoms and outcome were also recorded

Methods

Microbial identification was performed by Minitek (Becton Dickinson) systems until 1993 and with Vitek Jr identification system (Vitek, Bio Mérieux) since 1993. Routine blood culturing has been used since 1990. MIC for isolated organisms were determined according to the NCCLS standards after 1992, and before 1992 with a disk diffusion method. The antimicrobials tested for susceptibility, resistance and breakpoints are listed in Table 1.

Statistical analysis

Univariate analysis with X^2 test and Fisher's exact test were used to compare continuing variables and $P<0.05$ was considered as significant. Variables in subgroups of episodes caused by monomicrobial versus polymicrobial bacteremia were compared.

Antibiotic policy

In our cancer center, the antibiotic policy since 1990 has allowed the use of an oral quinolone (ofloxacin 200 mg bid) for prevention of infection, in afebrile neutropenic (<500 PMN/mL) patients with hematologic malignancy.

Ceftriaxone plus netilmicin or cefotaxime plus pefloxacin are used in febrile neutropenia for empiric therapy. In acute leukemia, amikacin plus ceftazidime are used as first-line therapy, and vancomycin is added in nonresponding fever, according to the Infectious Diseases Society of America (IDSA) guidelines. Imipenem has been used since 1991 in our center in nonresponding fever together with vancomycin and

Table 1. Susceptibility of *E. coli* to selected antimicrobial agents (1990–1995)

	Number of sensitive/total (%)						
	1990	*1991*	*1992*	*1993*	*1994*	*1995*	*Total*
AMP <32	0/4 (0)	2/10 (20.0)	4/23 (17.3)	5/19 (26.3)	12/20 (60.0)	6/28 (21.4)	29/115 (25.2)
CEFAZ <8	0/4 (0)	6/10 (10.0)	15/23 (65.2)	12/19 (63.1)	18/20 (90.0)	20/28 (71.4)	71/115 (61.8)
CTAZ <32	2/4 (50.0)	9/10 (90.0)	19/23 (82.7)	17/19 (89.5)	20/20 (100.0)	27/28 (96.4)	104/115 (90.4)
CTRX <32	2/4 (50.0)	8/10 (80.0)	19/23 (82.7)	16/19 (84.2)	20/20 (100.0)	26/28 (92.9)	101/115 (87.8)
CFUR <32	2/4 (50.0)	8/10 (80.0)	18/23 (78.3)	16/19 (84.2)	20/20 (100.0)	26/28 (98.9)	101/115 (87.8)
CTAX <32	2/4 (50.0)	8/10 (80.0)	19/23 (82.7)	16/19 (84.2)	20/20 (100.0)	26/28 (92.9)	102/115 (88.7)
OFL <8	4/4 (100.0)	10/10 (100.0)	23/23 (100.0)	19/19 (100.0)	20/20 (100.0)	26/28 (92.9)	113/115 (98.3)
GEN <8	2/4 (50.0)	7/10 (70.0)	18/23 (78.3)	15/19 (78.9)	20/20 (100.0)	28/28 (100.0)	101/115 (87.8)
NET <8	2/4 (50.0)	8/10 (80.0)	20/23 (86.9)	16/19 (84.2)	20/20 (100.0)	28/28 (100.0)	105/115 (91.3)
TOB <8	2/4 (50.0)	6/10 (60.0)	19/23 (82.7)	15/19 (78.9)	20/20 (100.0)	27/28 (96.4)	100/115 (86.9)
AMI <16	4/4 (100.0)	8/10 (80.0)	12/23 (52.1)	15/19 (78.9)	20/20 (100.0)	28/28 (100.0)	98/115 (85.2)
TIC <32	1/4 (25.0)	ND	ND	ND	19/20 (91.0)	20/28 (71.4)	40/52 (78.5)
MER <8	ND	ND	ND	18/19 (94.7)	20/20 (100.0)	28/28 (100.0)	66/67 (98.5)
CIP <8	ND	ND	23/23 (100.0)	19/19 (100.0)	20/20 (100.0)	26/28 (92.9)	88/90 (97.8)
COT <32	2/4 (50.0)	9/10 (90.0)	20/23 (86.9)	19/19 (100.0)	19/20 (91.0)	24/28 (85.7)	104/115 (90.4)

Abbreviations: CMP – chloramphenicol, AMP – ampicillin, STM – streptomycin, GEN – gentamicin, TOB – tobramycin, NET – netilmicin, AMI – amikacin, CFUR – cefuroxime, CEFAZ – cefazoline, CTAZ – ceftazidime, AZL – azlocillin, TIC – ticarcillin, OFL – ofloxacin, COL – colymicine, COT – cotrimoxazole, MER – meropenem, CIP – ciprofloxacin, CTRX – ceftriaxone, CTAX – cefotaxime

Table 2. Etiology of bacteremia and fungemia at the National Cancer Institute in 1989–1995

	1989	*1990*	*1991*	*1992*	*1993*	*1994*	*1995*	*Total*
Number of admissions (A)	1205	1490	1545	1615	1970	2161	2315	12301
No. of bacteremic episodes (E) (%E/A)	26 (2,1%)	36 (2,4%)	78 (5%)	121 (7,1%)	158 (8%)	239 (11,1%)	211 (9,1%)	869
Number of Blood cultures obtained	435	895	2001	2687	2516	2505	3280	14479
Deaths due to bacteremia	9	10	9	10	13	12	14	77
Deaths per episode (%)	33,3%	27,7%	11,5%	3,6%	8,2%	3,0%	2,4%	8,9%
Prophylaxis with ofloxacin	–	–	+	+	+	+	+	
Prophylaxis with fluconazole	–	–	–	+	+	+	+	
Prophylaxis with V-penicillin	–	–	–	–	–	+	+	
Therapeutic regimens most frequently used	OXA+GEN CTAX+GEN CTAZ+AMI	CTAZ+AMI CTAX+GEN	CTRX+NET CTAZ+AMI	CTAZ+AMI CTRX+NET	CTRX+NET CTAZ+AMI	CTAZ+AMI CTRX+NET	CTAZ+AMI CTRX+NET	

Abbreviations: OXA – oxacillin, GEN – gentamicin, AMI – amikacin, CTAZ – ceftazidime, CTAX – cefotaxime, CTRX – ceftriaxone, NET – netilmicin

amikacin or colimycin, only after failure of first line therapy, or for documented systemic *Pseudomonas aeruginosa* infections, with amikacin or colimycin.

Definitions

(a) *Bacteremia* was defined by the isolation of *E. coli* from two or more blood cultures or from a single blood culture if there was a clinically apparent and/or culture-positive other source of infection.
(b) *Source of bacteremia* was defined as a culture-positive site or a clinically apparent site of infection. If blood was the only culture-positive specimen and there was no apparent source of infection, the source of bacteremia was considered unknown.
(c) *Polymicrobial bacteremia* was defined by the isolation of organisms in addition to *E. coli* either from the same blood culture or from multiple cultures performed during a single bacteremic episode.
(d) Patients were considered *neutropenic* if their absolute neutrophil count was $<500/mm^3$ at the onset of bacteremia.
(e) *Septic shock* was defined by sepsis associated with evidence of organ hypoperfusion and a systolic blood pressure that was <90 mmHg or >30 mmHg less than the baseline value, or intravenous fluids or vasopressors were needed to maintain blood pressure.
(f) *Mortality from bacteremia* (*attributable mortality*) was defined as death with clinical signs of active infection and a positive blood culture result.
(g) *Death*, appearing up to five days after a bacteremic episode, but not clearly associated with sepsis and/or shock, was considered as death with bacteremia (*crude mortality*).
(h) *Relapse* was defined as a positive blood culture appearing within 10 days after initial improvement or cure.

RESULTS

Incidence and etiology

From 2000 bacterial isolates from blood cultures in cancer patients between January 1, 1989 and December 31, 1995 hospitalized in the 360 bed National Cancer Institute (Table 2), reference cancer institute for the Slovak Republic (5.5 million population), 506 (26.8%) were Gram-negative bacteria; 115 (20.8%) of Gram-negative bacteria were due to *E. coli*. *E. coli* was the second most common isolate from blood cultures in our cancer patients (after *Pseudomonas aeruginosa*). The proportion of *E. coli* among Gram-negative bacteremia cases in 1989–1995 was 20.8%, and varied from 12.4% (1994) to 36.3% in 1990 (Table 2, Table 3).

Risk factors and outcome

The commonest risk factors in *E. coli* bacteremia cases in our cancer patient population were: solid tumors as the underlying disease (70.7%), previous chemotherapy (44.6%) and prior surgery within 10 days (46.2%), and vascular catheter insertion (32.3%); 69.2% were monomicrobial. The overall cure rate was 76.9%, and the attributable mortality was 17%.

Third-generation cephalosporins alone or in combination with an aminoglycoside were the most common treatment regimens. Six patients with monomicrobial bacteremia were not cured using antibiotic therapy, but were cured by catheter removal (Table 4).

Comparison of monomicrobial to polymicrobial episodes

When 45 monomicrobial episodes were compared with 20 polymicrobial episodes (where *E. coli* was found in blood cultures together with *Streptococcus viridans*, *Enterococcus* spp., *Candida* spp., coagulase-negative staphylococci, *Klebsiella* spp. or *Pseudomonas*

Table 3. Trends in etiology of Gram-negative bacteremias within 1989–1995

	Number of isolates per year (%)							
G-bacteria	*1989*	*1990*	*1991*	*1992*	*1993*	*1994*	*1995*	*Total*
Pseudomonas aeruginosa	5 (71.4)	0 (0)	5 (9.2)	20 (21.8)	22 (28.5)	46 (30.7)	41 (35.6)	139 (27.5)
E. coli	1 (14.3)	4 (36.3)	10 (18.5)	23 (25.0)	19 (24.7)	20 (12.4)	28 (24.3)	115 (20.8)
Acinetobacter calcoaceticus	1 (14.3)	0 (0)	11 (20.3)	12 (13.0)	10 (13.0)	17 (11.3)	11 (9.5)	62 (12.2)
Klebsiella spp.	0 (0)	6 (54.5)	20 (37.0)	6 (6.5)	7 (9.1)	12 (8.0)	10 (8.7)	61 (12.1)
Enterobacter spp.	0 (0)	0 (0)	2 (3.7)	10 (10.9)	5 (6.5)	24 (16.0)	10 (8.7)	51 (10.1)
Stenotrophomonas maltophilia	0 (0)	0 (0)	0 (0)	10 (10.9)	6 (7.8)	7 (4.7)	8 (7.0)	31 (6.1)
Proteus spp.	0 (0)	0 (0)	3 (5.6)	3 (3.3)	8 (10.4)	9 (6.0)	2 (1.7)	25 (4.9)
Pseudomonas cepacia	0 (0)	0 (0)	0 (0)	5 (5.4)	0 (0)	10 (6.7)	0 (0)	15 (2.9)
Flavobacterium spp.	0 (0)	0 (0)	4 (7.4)	0 (0)	0 (0)	0 (0)	1 (0.9)	5 (0.9)
Alcaligenes fecalis	0 (0)	1 (9.2)	0 (0)	0 (0)	0 (0)	3 (2.0)	0 (0)	4 (0.8)
Citrobacter spp.	0 (0)	0 (0)	1 (1.9)	0 (0)	0 (0)	1 (0.7)	2 (1.7)	4 (0.8)
Serratia spp.	0 (0)	0 (0)	0 (0)	1 (1.1)	0 (0)	1 (0.7)	2 (1.7)	4 (0.8)
Hafnia alvei	0 (0)	0 (0)	0 (0)	1 (1.1)	0 (0)	0 (0)	0 (0)	1 (0.2)
Salmonella spp.	0 (0)	0 (0)	0 (0)	1 (1.1)	0 (0)	0 (0)	0 (0)	1 (0.2)
Gram-negative bacteria (total)	7 (17.5)	11 (12.3)	54 (32.0)	92 (28.6)	77 (21.6)	150 (30.9)	115 (26.4)	506 (26.8)

aeruginosa), only acute leukemia and breakthrough bacteremia were more frequently associated with polymicrobial *E. coli* episodes. Septic shock (50 vs 8.9%, P<0.005) and attributable mortality(35.0 vs 8.9%, P<0.03) were significantly higher among polymicrobial than monomicrobial *E. coli* episodes (Table 4).

Susceptibility to antimicrobials

Table 1 shows the susceptibility of 115 strains of *E. coli* to antibiotics causing 65 bacteremic episodes in 1990–1995. The lowest resistance rates were observed for ciprofloxacin and ofloxacin (98.3%), meropenem (98.5%), colimstin (93.9%) and netilmicin (91.3%). Annual percentages of resistant strains did not show any significant changes in 1994–1995 in comparison with 1990–1991. Only two quinolone-resistant *E. coli* were observed, both in 1995. Resistance to cefotaxime is decreasing.

DISCUSSION

The incidence of *E. coli* bacteremia was stable from 1990 to 1995; however, after the introduction of quinolones, mortality from bacteremia decreased more than 10-fold, from 33.30 (1990) to 2.4% (1995). Attributable mortality from *E. coli* was higher (17%) but when monomicrobial bacteremia from *E. coli* infection alone was taken into account, associated mortality was only 8.9%, which is lower than that reported from other centers.[1,2,7] However, when *E. coli* caused bacteremia together with other bacteria (20 of polymicrobial episodes were due to *E. coli* plus enterococci, staphylococci, *Klebsiella pneumoniae*, yeasts, pseudomonads), the mortality from bacteremia was significantly higher (35.0%) and similar to other gram-negative bacilli.[3,8]

Resistance to quinolones in our institute was relatively low in comparison with other surveillance studies from cancer centers.[1,2] Only two bacteremic episodes were due to ofloxacin and ciprofloxacin (MIC >8 mmol/L)-resistant *Enterobacter cloacae*. This is surprisingly low (despite the use of oral ofloxacin in prevention of infection in patients with hematologic malignancies since 1990) and may be because of limited use of quinolones in therapy. We did not observe any outbreaks of quinolone-resistant *E. coli* as reported from other cancer centers with a similar prophylactic strategy.[3,4] Most *E. coli* bacteremic episodes appeared in

Table 4. *E. coli* bacteremia in cancer patients. Risk factors and outcome: monomicrobial versus polymicrobial bacteremias

	Total	*Monomicrobial*	*Polymicrobial*	*P<*
No. of pts.	65	45	20	
Risk factors				
Males	36 (55.4)	25 (55.5)	11 (55.0)	NS
Females	29 (44.6)	20 (45.5)	9 (45.0)	NS
Age >60	25 (38.5)	19 (42.2)	6 (30.0)	NS
Underlying disease				
—Acute leukemia	12 (18.5)	4 (8.9)	8 (40.0)	0.005
—Other hematologic malignancies	7 (10.8)	6 (13.4)	1 (5.0)	NS
—Solid tumors	46 (70.0)	35 (77.7)	11 (55.0)	NS
Neutropenia <500 (N)	13 (20.0)	9 (20.0)	4 (20.0)	NS
Previous chemotherapy	29 (44.6)	17 (37.8)	12 (60.0)	NS
Diabetes mellitus	5 (7.7)	3 (6.7)	2 (10.0)	NS
Previous surgery	30 (46.2)	22 (48.9)	8 (40.0)	NS
Previous endoscopy	8 (12.3)	6 (13.4)	2 (10.0)	NS
Central venous catheter	21 (32.3)	17 (37.8)	4 (20.0)	NS
Urinary tract catheter	15 (23.1)	11 (24.4)	4 (20.0)	NS
Source of bacteremia				
—Urinary tract	8 (12.3)	6 (13.4)	2 (10.0)	NS
—Gastrointestinal tract	9 (13.9)	6 (13.4)	3 (15.0)	NS
—Infected wound	7 (10.8)	3 (6.7)	4 (20.0)	NS
—Infected catheter	6 (9.2)	2 (4.2)	4 (20.0)	NS
Prior colonization	8 (12.3)	7 (15.6)	1 (5.0)	NS
No of positive cultures/patients/cultures ratio	115/65	61/61/45 =1.36	54/54/20 =2.7	—
Breakthrough bacteremia	20 (30.8)	2 (4.2)	18 (90.0)	0.001
—OFL resistant	2 (3.1)	1 (2.1)	1 (5.0)	NS
—during OFL prophylaxis	4 (6.1)	2 (4.2)	2 (10.0)	NS
—during empiric therapy	17 (24.7)	1 (2.1)	16 (80.0)	0.001
—with AMO/CLAV	4 (6.1)	0 (0)	4 (20.0)	—
—with NET+CTAX	4 (6.1)	0 (0)	4 (20.0)	—
—with AMI+CTAZ	6 (9.2)	0 (0)	6 (30.0)	—
Outcome				
Cure	50 (76.9)	38 (84.4)	12 (60.0)	0.05
Death due to underlying disease	4 (6.1)	3 (6.7)	1 (5.0)	NS
Death due to bacteremia	11 (17.0)	4 (8.9)	7 (35.0)	0.03

non-neutropenic patients (80.0% of episodes were in non-neutropenic patients) in contrast to *Streptococcus viridans*, *Enterococcus faecalis*, and *Pseudomonas aeruginosa*, which caused bacteremia more frequently in neutropenic patients with acute leukemia.[2,5–7]

Prior surgery as a common risk factor for *E. coli* for both cancer and non-cancer patients is reported worldwide[2,5,6] and occurred in 46.2% bacteremic episodes caused by *E. coli* in our patient population.

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