CLINICAL MICROBIOLOGY

Risk factors, aetiology, therapy and outcome in 123 episodes of breakthrough bacteraemia and fungaemia during antimicrobial prophylaxis and therapy in cancer patients

S. SPANIK, J. TRUPL[‡], A. KUNOVA*, L. DRGONA[†], T. SALEK, J. MARDIAK, E. KUKUCKOVA*, M. STUDENA*, P. PICHNA[†], E. ORAVCOVA, E. GREY, P. KOREN*, J. SVEC[§], J. LACKA, J. SUFLIARSKY and V. KRČMERY

*St Elizabeth National Cancer Institute, Bratislava, *Department of Medicine, University of Trnava, †Department of Chemotherapy, Postgraduate Medical School, ‡Department of Microbiology, Hematology and Medicine, National Cancer Institute and §Department of Oncology, Medical School, Comenius University, Bratislava, Slovak Republic*

One hundred and twenty-three breakthrough bacteraemias (BB) were defined during a 5-year period in a National Cancer Centre, among 9986 admissions and a total of 979 bacteraemic episodes analysed. Of 123 bacteraemias in 103 patients, 77 were polymicrobial and 116 of the 323 organisms isolated were resistant to currently administered antimicrobial agents. Sixty-seven of the bacteraemic episodes were catheter-associated, as confirmed by the isolation of the same organisms from both blood and catheter tip. The strains isolated most frequently were coagulase-negative staphylococci (30.5%), corynebacteria (10%), *Pseudomonas aeruginosa* (10%), *Enterococcus faecalis* (9%) and viridans streptococci (8.5%). Gram-positive aerobes accounted for two-thirds of all micro-organisms isolated during breakthrough bacteraemic and fungaemic episodes. Polymicrobial episodes were associated more frequently with vascular catheters and neutropenia, and had a less favourable outcome than monomicrobial infections. Relapse was associated more frequently with catheter-related episodes, but the overall mortality rate was similar and independent of catheter insertion. Breakthrough bacteraemic and fungaemic episodes were associated more frequently with acute leukaemia. Catheter removal, as an independent variable, and modification of antimicrobial therapy were essential for better outcome.

Introduction

The incidence of bacteraemia and fungaemia has increased steadily during the past decade, despite the use of broad-spectrum empiric therapy with bactericidal drugs. Recent EORTC studies showed that bacteraemic episodes were associated more frequently with therapy failure and a worse outcome was observed in polymicrobial and intravascular catheter-associated bacteraemia and fungaemia [1–7]. In large studies on prevention and therapy of febrile neutropenia, breakthrough bacteraemias (BB) are increasingly common [4–8]. Several outbreaks of BB and fungaemia have

been reported from cancer centres worldwide either due to quinolone-resistant Enterobacteriaceae [9–11], vancomycin-resistant enterococci [12], penicillin-resistant viridans streptococci [13], meropenem-resistant *Pseudomonas* spp. [14] or to azole-resistant *Candida* spp. [15, 16].

Mortality following gram-positive bacteraemia, with the exception of viridans streptococci, is low [3–7]. Once quinolones were introduced into the prophylactic regimen, the incidence and mortality following gram-negative bacteraemia decreased, although fungaemia is still associated with 25–40% mortality.

Apart from catheters (as a source of persisting bacteraemia), infection with resistant strains and neutropenia are recognised risk factors for breakthrough bacteraemia and fungaemia in cancer patients.

The aim of this study was to investigate the incidence, aetiology, risk factors and outcome of BB over 5 years in the National Cancer Centre of the Slovak Republic.

Patients and methods

A total of 979 bacteraemic and fungaemic episodes among 9986 admissions between 1 Jan. 1990 and 31 Dec. 1994 (5 years) at the 500-bed National Cancer Institute of the Slovak Republic were analysed to assess breakthrough bacteraemic and fungaemic episodes. There were 123 episodes of BB in 103 patients, with 323 isolates from blood cultures. BB was defined by a positive blood culture drawn through a peripheral vein, following symptoms, during antibiotic therapy or prophylaxis with absorbable drugs. Patients with haematological malignancies and neutropenia $<500/\text{ml}$ routinely receive ofloxacin plus fluconazole or itraconazole orally. Blood cultures were drawn from a peripheral vein and the catheter, only on suspicion of a vascular catheter-associated BB or fungaemic episode. The catheter was removed routinely when positive blood cultures or polymicrobial BB appeared, except in the case of five patients with thrombocytopenia $<20\,000/\text{ml}$. Routine blood culture was performed by the BACTEC system (Becton Dickinson). Antibiotic susceptibility testing was performed according to the NCCLS methods.

Catheter-associated BB was defined when the same organism(s) were isolated from blood culture and catheter tip. Polymicrobial BB was defined as the isolation of two or more different species from blood culture.

Neutropenia was defined by a neutrophil count of persistently $<500/\text{ml}$ at the time a blood culture was taken.

Cure was accepted if patients' signs and symptoms disappeared. Failures included relapse, or death during or because of bacteraemia or fungaemia. Relapse was defined by a second episode within 10 days during one hospitalisation. Death during BB was not always clearly associated with sepsis. On the other hand, where death occurred BB or within 5 days of an episode and followed clinically documented sepsis it was deemed a treatment failure (death due to bacteraemia or fungaemia).

Risk factors associated with BB, such as underlying disease, neutropenia, presence of central or peripheral venous catheter or presence of resistant isolates in blood culture were recorded. Aetiology, therapy and outcome of patients with BB were also recorded.

For statistical analysis the χ^2 test was used to compare different subgroups and $p < 0.05$ was considered a significant difference.

Results and discussion

The incidence and distribution of BB are outlined in Table 1: among 9986 admissions, there were 979 bacteraemic and fungaemic episodes and 123 (13%) were breakthrough (BB). Of the latter, approximately one-half were vascular catheter-associated and two-thirds were polymicrobial.

Patient details, underlying disease, isolated micro-organism, antibiotic therapy, onset of bacteraemia, risk factors (e.g., catheter, neutropenia, microbial resistance), therapy and outcome are shown in Tables 2–4, separately for monomicrobial and polymicrobial, and vascular catheter-associated BB. Tables 2–4 show the assessment of risk factors for catheter-associated BB. Study of the risk of vascular catheter-associated and non-vascular catheter-associated bacteraemia indicated that there was no difference between the groups in the appearance of BB during therapy or prophylaxis (80.6 and 78% BB appeared during therapy and 19.4 and 25% during prophylaxis with ofloxacin, respectively). There was a higher incidence of neutropenia or resistant organisms or both in non-vascular catheter-associated BB when compared with catheter-related BB. Other risk factors such as neutropenia or identification of resistant strains from blood cultures, or both, were more frequently associated with the group of vascular catheter-associated BB.

There were similar cure rates (51.2% in all patients with BB) with no significant difference between catheter- and non-catheter-related BB, although there was a higher relapse rate while a vascular catheter was *in situ* (14.9% versus 7.1%, $p < 0.03$). Surprisingly, death due to bacteraemia or septic shock was more frequently registered in patients without catheters. When analysing therapy and action taken in BB, with and without vascular catheter, the failure rate was 100% in those where no action or therapy was taken. There was no difference in outcome, once the catheter was removed, whether or not antibiotic therapy was modified. This finding suggests that catheter removal is essential for cure. Change of antimicrobial agent alone, in the group of patients

Table 1. Distribution of breakthrough bacteraemic episodes among 979 bacteraemic and fungaemic episodes within 5 years among 9986 admissions

Criteria	Number of patients
Admissions (1.1.1989–31.12.1994)	9986
Patients with bacteraemia	443
Bacteraemic episodes (BE)	979
Breakthrough bacteraemia episodes (BB)	123
Strains isolated from BB	323
Vascular catheter-associated BB	67 (54.5%)
Non-vascular catheter-associated BB	56 (45.5%)
Monomicrobial BB	46 (37.4%)
Polymicrobial BB	77 (62.6%)

Table 2. Breakthrough bacteraemia (BB) in 123 patients: its relationship with other risk factors and catheter association

Criteria	Total	Catheter-associated bacteraemia	Non-catheter-associated bacteraemia	p value
Number of patients	123	67	56	
BB during therapy	96 (78%)	54 (80.6%)	42 (75%)	NS
BB during prophylaxis	27 (22%)	13 (19.4%)	14 (25%)	NS
Underlying disease				
Acute leukaemia	67 (54.5)	45 (67.2)	22 (39.3)	0.02
Other haematological disorders	22 (17.9)	11 (16.4)	11 (19.6)	NS
Solid tumours	34 (27.6)	11 (16.4)	23 (41.1)	0.02
Risk factors				
Catheter only	9 (7.3)	9 (13.4)	0	0.001
Neutropenia only	7 (5.7)	0	7 (12.5)	0.001
Resistant organism only	14 (11.4)	0	14 (25)	0.001
Neutropenia + resistance	35 (28.5)	0	35 (62.5)	0.001
Catheter + neutropenia	30 (24.4)	30 (44.8)	0	0.001
Catheter + resistance	9 (7.3)	9 (13.4)	0	0.001
Catheter + resistance + neutropenia	19 (15.4)	19 (28.4)	0	0.001
Therapy				
Antibiotic change/failures	47/20 (42.5)	0	47/20 (42.5)	0.001
Catheter extracted + antibiotic not changed/failures	9/2 (22.2)	9/2 (22.2)	0	0.001
Catheter extracted + antibiotic changed/failures	58/29 (50)	58/29 (50)	0	0.001
No therapy/failures	9/9 (100)	0	9/9 (100)	0.001
Aetiology				
G ⁺	55 (44.8)	23 (34.3)	32 (57.1)	0.04
G ⁻	22 (17.8)	10 (14.9)	12 (21.4)	NS
Mixed G ⁺ and G ⁻ (fungi)	46 (37.4)	34 (50.8)	12 (21.4)	0.02
Outcome				
Cured	63 (51.2)	36 (53.8)	27 (48.2)	NS
Failures – cured but relapsed	14 (11.4)	10 (14.9)	4 (7.1)	0.03
– death with bacteraemia	18.1 (14.6)	9 (13.4)	9 (16.1)	NS
– death due to bacteraemia (septic shock)	28 (22.8)	12 (17.9)	16 (28.6)	0.03

G⁺, gram-positive bacteria; G⁻, gram-negative bacteria.

Table 3. Breakthrough bacteraemia (BB) in 123 patients: risk factors associated with monomicrobial and polymicrobial BB

Criteria	Monomicrobial (%)	Polymicrobial (%)	p value
BB occurring during therapy for BB	36 (78.3)	60 (77.9)	NS
BB occurring during prophylaxis	10 (21.7)	17 (22.1)	NS
Underlying disease			
Acute leukaemia	20 (43.4)	47 (61)	0.05
Other haematological disorders	10 (21.8)	12 (15.6)	0.05
Solid tumours	16 (34.8)	18 (23.4)	0.03
Risk factors			
Catheter only	5 (10.9)	4 (5.2)	0.03
Neutropenia only	4 (8.7)	3 (3.9)	0.03
Resistant organism only	7 (15.2)	7 (9.1)	NS
Neutropenia + resistance	15 (32.6)	20 (26)	NS
Catheter + neutropenia	8 (17.4)	22 (28.6)	0.03
Catheter + resistance	3 (6.5)	6 (7.8)	NS
Catheter + resistance + neutropenia	4 (8.7)	15 (19.5)	0.03
Therapy			
Antibiotic change (cure/failure)	22/9	25/11	–
Catheter extracted (cure/failure)	9/2	0/0	–
Catheter extracted + antibiotic change (cure/failure)	11/5	47/24	–
No therapy (cure/failure)	4/4	5/5	–
Aetiology			
G ⁺	27 (58.7)	28 (36.4)	NS
G ⁻	19 (41.3)	3 (3.9)	0.005
Mixed G ⁺ and G ⁻ (fungi)	0/0	46 (59.7)	0.0001
Outcome			
Cured	26 (56.3)	37 (48)	NS
Failures – cured but relapsed and died	6 (13.1)	8 (10.4)	NS
– death with bacteraemia	6 (13.1)	12 (15.6)	NS
– death due to bacteraemia (septic shock)	8 (17.5)	20 (26)	NS
Number of patients (total = 100%)	46	77	

G⁺, gram-positive bacteria; G⁻, gram-negative bacteria.

Table 4. Breakthrough bacteraemia (BB) in 123 patients: risk factors related to outcome

	Total	Cured patients (%)	Failed (died or relapsed) (%)	Died	Cured but relapsed	
Time of BB						
BB occurring during therapy for BB	96	49 (77.8)	47 (78.3)	39	8	NS
BB occurring during prophylaxis	27	14 (22.2)	13 (21.7)	7	6	NS
Underlying disease						
Acute leukaemia	67	37 (58.9)	30 (50)	19	11	NS
Other haematological disorders	22	8 (12.7)	14 (23.3)	12	2	NS
Solid tumours	34	18 (28.6)	16 (26.6)	15	1	NS
Risk factors						
Catheter-associated	67	36 (57.1)	31 (51.7)	21	10	NS
Non-catheter-associated	56	27 (42.8)	29 (48.3)	25	4	NS
Catheter only	9	8 (12.7)	1 (1.7)	1	0	0.01
Neutropenia only	7	2 (3.2)	5 (8.3)	5	0	0.01
Resistant organism only	14	7 (11.1)	7 (11.7)	7	0	NS
Neutropenia plus resistant organism	35	17 (27)	18 (30)	14	4	NS
Catheter plus neutropenia	30	15 (23.8)	15 (25)	11	4	NS
Catheter plus resistance	9	5 (7.9)	4 (6.7)	3	1	NS
Catheter plus resistance plus neutropenia	19	9 (14.3)	10 (16.7)	5	5	NS
Aetiology						
G ⁺ (polymicrobial)	28	15 (23.8)	13 (21.7)	8	5	NS
G ⁻ (polymicrobial)	3	0	3 (5)	2	1	0.01
Mixed G ⁺ and G ⁻ (polymicrobial)	46	22 (34.9)	24 (40)	18	6	NS
G ⁺ (monomicrobial)	27	13 (20.1)	14 (23.3)	10	4	NS
G ⁻ (monomicrobial)	19	13 (20.1)	6 (10)	4	2	NS
Number of patients (total = 100%)	123	63	60	42	18	
Therapy/action						
Antibiotic change	47	27 (42.8)	20 (33.3)	16	4	NS
Catheter extraction antibiotic not changed	9	7 (11.1)	2 (3.3)	1	1	0.01
Catheter extracted plus antibiotic changed	58	29 (46.1)	29 (48.3)	20	9	NS
No therapy/no action	9	0	9 (15)	9	0	0.001

G⁺, gram-positive bacteria; G⁻, gram-negative bacteria.

without vascular catheters, was as effective as catheter removal plus antibiotic change in patients with a vascular catheter.

Table 3 shows the relationship between risk factors and outcome in monomicrobial BB and polymicrobial BB; no difference between the groups was observed when BB occurred during therapy or prophylaxis. The majority of monomicrobial and polymicrobial (78.3 and 77.9%) BB appeared during therapy. No patients had both polymicrobial plus monomicrobial BB on different occasions. Polymicrobial BB occurred rather more frequently in patients with acute leukaemia (AL) (61.0% patients with polymicrobial BB had AL while 43.4% with monomicrobial BB had AL). A statistically significant risk for polymicrobial BB was the presence of neutropenia plus catheter or isolation of resistant strains, or both (19.5% polymicrobial *versus* 8.7% monomicrobial BB, $p < 0.03$). Failure was independent of therapy and action taken except for catheter removal (catheters were removed in only nine cases of monomicrobial BB, and the relapse rate was only 22.2% compared with a total of 43–52% failures). Change of antimicrobial agents only in both monomicrobial and polymicrobial BB was equally unsuccessful (43 *versus* 44%, not significant).

Monomicrobial BB was more frequently associated with gram-positive (51.7%) than gram-negative organisms (41.3%), but in polymicrobial BB 36.4% were due to two or more gram-positive species, only 3.9%

were due to two gram-negative species and 59.7% to mixed aetiology.

There was no statistically significant difference in rates of cure, relapse and death, between monomicrobial polymicrobial BB. This was an unexpected finding, because polymicrobial bacteraemia in similar studies has been associated more often with failure [5–8, 16].

Table 4 shows the association between outcome and various risk factors: there was no significant difference in outcome if BB occurred during prophylaxis or therapy if the patient had AL or other malignancy (haematological or solid tumour). More patients failed in the subgroup of polymicrobial BB than monomicrobial BB when BB was caused by a resistant strain ($p < 0.04$) or a gram-negative organism. Higher cure rates were observed in patients with BB after catheter extraction, whether or not antimicrobial agents were changed, as already observed in the analyses in Tables 2 and 3. This confirms the importance of catheter removal for a successful outcome.

Table 5 shows the association between the antibiotic resistance of the organisms and the antibiotic regimen during which BB appeared. During ofloxacin prophylaxis, 11 vascular catheter-associated and nine non-catheter-associated BB were noted, most frequently caused by coagulase-negative staphylococci (CNS),

Table 5. Association between antibiotic susceptibility of breakthrough pathogen and antibiotic regimen

Pathogen occurring during antimicrobial therapy (n)	Antibiotic susceptibility	Number of patients treated with antibiotic													
		PEF		CTR		CTAX	AMI	NET	GEN	CLIND	AMP/SULB AZI, PIP	FLU	IMIP	VAN	Total
		CIP	OFL	CTAZ	CTRX										
Coagulase-negative staphylococci (119)	S	5	12	10	4	3	1	2	1	0	2	12	52		
Viridans streptococci (26)	R	21	8	9	6	7	5	1	5	0	1	4	67		
	S	0	4	3	3	8	0	0	0	0	0	2	20		
Ent. faecalis (28)	R	2	3	0	0	0	0	0	0	0	0	1	6		
	S	2	0	0	1	1	1	1	1	0	0	1	8		
Corynebacterium spp. (32)	R	7	2	7	1	0	1	1	1	0	1	0	20		
	S	0	0	0	0	0	0	2	0	0	0	3	5		
Other gram-positive rods (3)	R	6	6	4	2	3	3	0	3	0	0	0	27		
	S	3	0	0	0	0	0	0	0	0	0	0	3		
E. coli (10)	R	0	0	0	0	0	0	0	0	0	0	0	0		
	S	4	0	1	0	1	2	0	0	0	0	0	8		
Klebsiella spp. (6)	R	0	0	0	0	0	0	0	0	2	0	0	2		
	S	1	1	2	0	0	2	0	0	0	0	0	6		
Enterobacter spp. (22)	R	0	0	0	0	0	0	0	0	0	0	0	0		
	S	4	2	4	4	1	1	0	0	0	0	0	16		
Ps. aeruginosa (32)	R	1	0	3	0	0	1	0	0	1	0	0	6		
	S	6	3	3	0	5	0	0	0	0	0	5	17		
Acinetobacter spp. (23)	R	6	6	3	0	1	1	0	0	2	0	0	20		
	S	0	1	0	2	2	0	0	0	0	0	0	5		
Stenotrophomonas spp. (13)	R	3	4	5	1	1	1	1	1	1	0	0	18		
	S	2	1	0	1	0	0	0	0	0	0	0	4		
Stenotrophomonas spp. (13)	R	3	1	2	0	1	1	0	0	0	1	0	9		
	S	1	0	1	1	0	1	0	0	1	0	0	5		
Candida spp. (4)	R	0	0	0	0	0	0	0	0	0	0	0	0		
	S	0	0	0	0	0	0	0	0	0	0	0	0		
Total (323)	R	28	24	24	16	21	8	5	2	4	3	18	153		
	S	49	30	33	10	13	13	3	14	0	5	5	175		

S, sensitive to antibiotics; R, resistant. PEF, pefloxacin; CIP, ciprofloxacin; OFL, ofloxacin; CTAX, ceftriaxone; CTX, cefotaxime; AMI, amikacin; NET, netilmicin; GEN, gentamicin; CLIND, clindamycin; AMP/SULB, ampicillin sulbactam; AZI, azlocillin; PIP, piperacillin; FLU, fluconazole; IMIP, imipenem; VAN, vancomycin.

Enterococcus faecalis, viridans streptococci, or *Ps. aeruginosa*.

During therapy with quinolones (parental ofloxacin, ciprofloxacin or perfloxacin), the most common breakthrough organisms were: CNS (five quinolone sensitive, 21 resistant strains), *Ps. aeruginosa* (six sensitive, six resistant), *Ent. faecalis* (two sensitive, seven resistant), *Stenotrophomonas maltophilia* (two sensitive, three resistant), *Corynebacterium* spp. and others (Table 5).

Despite therapy with ceftazidime (CTAZ), 44 organisms were isolated: 20 were CNS, seven viridans streptococci, nine *Ps. aeruginosa* (six CTAZ-resistant, three CTAZ-sensitive) and six *Corynebacterium* spp.

During therapy with cefotaxime (CTAX) or ceftriaxone (CTRX), the most frequently isolated strains among BB were CNS (19 strains, nine resistant), *Ent. faecalis* (seven, all resistant), *Enterobacter* spp. (seven strains, three CTAX- or CTRX-resistant), *Ps. aeruginosa* (six, three resistant).

During therapy with aminoglycosides 81 organisms were isolated: amikacin 26, netilmicin 34 and gentamicin 21 and the most commonly isolated organisms were CNS (26 strains), viridans streptococci (11), *Ps. aeruginosa*, *Acinetobacter* and surprisingly also *Enterobacter* spp. (seven each).

During therapy with penicillins (ampicillin sulbactam, azlocillin, piperacillin) BB occurred in only 16 cases, mostly due to CNS. Of eight strains breaking through therapy with imipenem, five were resistant to the antibiotic (one *Acinetobacter* sp., one *Sten. maltophilia*, one *Ps. aeruginosa*, one *Ent. faecalis*, one CNS). Surprisingly, 23 BB due to gram-positive bacteria also occurred during vancomycin (VAN) therapy, and five were VAN-resistant (*S. epidermidis* four strains, one viridans streptococcus), which is an unusual finding; *S. epidermidis* strains had MICs of VAN of 8–32 mg/L and the viridans streptococcus 16 mg/L. However, no BB due to VAN-resistant *Ent. faecalis* was observed, unlike other cancer centres [12].

CNS were the most frequent cause of BB and appeared in 116 (31.5%) of 322 blood cultures. Also common causes of BB were *Ps. aeruginosa* and *Corynebacterium* spp., 32 episodes each (9.9%) and *Ent. faecalis* (28 episodes).

In similar studies of BB [2–7], the most frequent risk factors were venous or urinary catheters along with persisting bacteraemia, age, diabetes mellitus, neoplasia and resistance of strains isolated during bacteraemia. In contrast to those studies, no clear benefit was observed in the immunosuppressed population following early change of therapy. In all those studies, if bacteraemia and fungaemia appeared catheter

extraction (if present) was independently beneficial for outcome. Optimal therapy duration for episodes is recommended to be up to 14 days [18–20].

Although VAN-resistance in viridans streptococci and CNS is rare in comparison to *Ent. faecium*, four resistant CNS and one VAN-resistant viridans streptococcus strain were observed, which has not been reported in other studies. This may be due to increased use of VAN in our centre, when use of VAN in 1994 was eight times that used in 1990.

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