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Antibiotic-resistant Bacteria in Hospitalized Patients with Bloodstream infections: Analysis of Some Associated Factors

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Abstract

Background: Blood infections are life-threatening if not detected and managed properly. This study investigates the correlation between fever and previous antibiotics therapy with differential time to positivity (DTP) at admitted patients at Nemazee Hospital in Shiraz, southern Iran.

Methods: From January 2005 to December 2006, 985 positive blood samples in Bactec bottles from the admitted patients at Nemazee Hospital were analyzed. Sensitivity patterns of the bacteria to a panel of antibiotics were determined by the disk diffusion method.

Results: *S. epidermidis, S. aureus* and *Acinetobacter* were the most prevalent isolates respectively. However, only 100 (20.7%) *S. epidermidis* samples were the true infections. The most susceptible Gram positive and negative bacteria were *S. viridance*, *S. aureus*, *H. influenzae*, and *Brucella spp.,* respectively. Imipenem, amikacin and ciprofloxacin were the effective ones against Gram negative bacteria, while vancomycin, co-amoxiclav and chloramphenicol were effective against Gram positive ones. Cefuroxime and penicillin G were less effective antibiotics against both Gram negative and positive bacteria.

Conclusion: As demonstrated, the combined prescription of vancomycin and imipenem seems to cover the majority of infective agents in the blood whenever an empirical therapy is to be initiated. Moreover, periodic surveillance of antibacterial susceptibility patterns is warranted.

Keywords: Bactec 9240; Differential time to positivity (DTP); Antibiotics susceptibility patterns; Fever, Iran

Introduction

Antibacterial susceptibility patterns for microorganisms isolated from the hospitalized patients with infectious diseases are continuously evolving.[1,2] These changes potentially lead to the emergence of antibiotics resistant isolates and treatment failures. Therefore, the treatment of patients with bacteremia is becoming more complicated in an era of increasing antimicrobial resistance among frequently occurring pathogens. Furthermore, in life-threatening conditions, timely initiation of appropriate antimicrobial therapy could be vital.[1] Bloodstream infection with bacteria is an example of such conditions associated with significant mortality and health-care costs. Fortunately, in the past decade, advances in refinement of both blood culture media and detection methods improved the detection of bloodstream infections.[3,4] BACTEC established in the studied hospital in 1999, is representative of such methods. It monitors increases in CO_2 concentration produced by growing microorganisms by means of a fluorescent sensor located in the bottom of each bottle.[5]

It has been shown that mortality associated with bacteremia is influenced by the administered antimicrobial agent. In the study by Weinstein *et al.*,[6]

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patients who received appropriate antimicrobial therapy during initial empirical therapy, after the blood culture was reported positive, and susceptibility results became available, had the lowest septicemia-associated mortality. Also, a low mortality rate was found in patients whose initial empirical therapy was not appropriate but changed after a positive report of the blood culture. Outcomes were poor for those patients whose antibiotics were not changed after the receipt of susceptibility test results or remained incorrect throughout the course of illness.[6]

The present prospective study was carried out to gain knowledge on the etiology and antimicrobial resistance patterns of bloodstream infections and to assess the association of fever, and previous antibiotic therapy with differential time to positivity (DTP). With this information available, the clinicians could be aware of the epidemiology of the bloodstream pathogens, their corresponding antibiotic resistance patterns and some associated risk factors which could consequently help them treat their patients appropriately and administer effective antibiotics whenever an empirical therapy needs to be considered.

Materials and Methods

This study was conducted between January 2005 and December 2006 at Nemazee Hospital affiliated to Shiraz University of Medical Sciences in Shiraz, southern Iran. This hospital is a tertiary care facility with 1000 beds located in Fars Province covering the patients from neighborhood provinces too. Patients suspicious to infections were categorized based on their clinical and paraclinical results. Treatments covered the possible causative Gram positive and negative microorganisms. If inappropriate, empirical therapy was initiated and the treatments were corrected based on culture results and antibiotic sensitivity tests.

Patients suspicious to blood infections who were admitted in ICUs, internal medicine, trauma and surgery wards were enrolled and blood samples were collected. Before sampling, the skin was disinfected with 70% isopropyl alcohol followed by 2% iodine tincture. Ten and 3 ml of blood from pediatric/neonate and adult patients under the supervision of specialists were taken and inoculated to BACTEC 9240 (Becton Dickinson Diagnostic Instrument Systems, Sparks, Md.) bottles peds plus/F or adult plus aerobic/F aseptically. An indication of patient's blood infection was confirmed by the corresponding specialist in each ward.

The bottles were incubated in Bactec system as recommended by manufacturer for 7 consecutive days. At the end of day 7, the negative bottles were removed from the instrument and subcultured similar to the positive ones described below. During the seven days of incubation, when the system alerted for positive results, 3 to 5 drops of blood culture samples were inoculated with 1 ml sterile syringe on the blood and chocolate agars containing 5% whole sheep blood and were incubated aerobically overnight. The pure culture was then stained by Gram method. An isolate was defined as an organism recovered from a blood culture bottle. A culture detected by Bactec 9240 and confirmed to be positive by both Gram stain and subcultures, was considered to be a true positive one. A culture that was instrument negative and negative upon terminal subculture was considered to be a true negative. Any culture that was instrument negative but positive upon terminal subculture was considered to be a false negative. Mean±standard deviation, and minimum and maximum of differential time to positivity (DTP) for the individual pathogen were then calculated.

Antibacterial susceptibility was determined according to standard disk diffusion (Kirby-Bauer) method, using Mast Co. (Mast Co, Merseyside, UK) or Difco (BBL, USA) disks. *E. coli* (ATCC 25922) and *S. aureus* (ATCC 25923) were used as controls for antibiotic susceptibility determination. Antibacterial susceptibility pattern was interpreted as recommended by Clinical Laboratory Standards Institute (formerly NCCLS).[7] Susceptibilities of Gram negative bacteria to the antibiotics including gentamicin (GM; 10 µg), amikacin (AN; 30 µg) cefalexin (KF; 30 µg) co-trimoxazole; (TS; 25 µg), cefuroxime (CXM; 30 µg), ceftriaxone (CRO; 30 µg), cefotaxime (CTX; 30 µg), imipenem; (IMI; 10 µg), cefixime (CFX; 5 µg), cefepime (CPM; 30 µg), ampcillin (AP; 10 µg), ceftazidime (CAZ; 30 µg), ciprofloxacin (CIP; 5 µg) and norfloxacin (NOR; 10 µg) were tested. Besides, susceptibilities of Gram positive bacteria to the antibiotics gentamicin (GM; 10 µg), penicillin G (PG, 10 unit), vancomycin (V; 30 µg) cefalexin (KF; 30 µg), co-trimoxazole (TS; 25 µg), oxacillin (OX; 1 µg), chloramphenicol (C; 30 µg), amoxicillin (AMO; 10 µg), erythromycin (E; 15 µg), ampicillin (AP; 10 µg), tetracycline (T; 30 µg), clindamycin (CD; 2 µg), ciprofloxacin (CIP; 5 µg), methicillin (MET; 5µg), tobramycin (TOB; 10 µg), co-amoxiclav (AMC; 30 µg) and kanamycin (KAN, 30 µg) were examined.

DTPs were expressed as mean±standard deviation, minimum and maximum. Statistical differences in DTPs of the bacteria isolated from febrile and afebrile patients and those who had previously received antibiotics with those who had not were calculated. The data were analyzed by SPSS, version 15, using independent sample *T* test and $p<0.05$ was considered significant.

Results

S. epidermidis, S. aureus, Acinetobacter spp., E. coli, Enterococcus spp. and *Enterobacter spp.* were more prevalent isolated bacteria sequentially. These bacteria are also mainly associated with nosocomial infections. Frequencies of the isolated bacteria from the blood samples and their corresponding DTPs are listed in Table 1. Due to variations in the level of bacteremia and differences in the generation time of the bacteria, DTP values were variable. *Brucella spp. with* DTP 65.5±32.7 and *Citrobacter spp.* with DTP 5.5±3.5 were standing at the highest and lowest levels, respectively. *S. epidermidis* was the main bacterium causing blood sample contamination. To differentiate between sample contamination and true infection, the acceptable criterion was to compare DTPs of the suspicious samples with the established values.[8] Accordingly, only 100 (20.7%) *S. epidermidis* isolates were true infections (Table 2). Effectiveness of the tested antibiotics against *H. influenzae*, *Brucella spp*, *Pseudomonas, Acinetobacter spp, Serratia spp., Kelbsiella spp.*, *Enterobacter spp.* and *E. coli* ranged from 83.5%, 82.3%, 54.0% 49.2% 49.0%, 48.7%, 47.5% to 41.8%, respectively. Susceptibility patterns of Gram positive bacteria to the tested antibiotics ranged from 66.2%, 65.6%, 63.4%, 54.3% to 33.4% corresponding to *S. viridance, S. aureus*, *S. pneumoniae*, *S. epidermidis* and *Enterococci spp.*, respectively. Antibiotic susceptibility patterns of Gram negative and Gram positive bacteria are displayed in Table 3 and 4. Effective antibiotics against Gram negative bacteria were imipenem, amikacin and ciprofloxacin, while for Gram positive bacteria, vancomycin, co-amoxiclav and chloramphenicol were the effective ones. In contrast, cefuroxime and penicillin G were less effective antibiotics against Gram negative and positive bacteria (Table 3 and 4). Data analysis did not show any significant statistical differences between DTPs of the bacteria isolated from the studied patients' samples (febrile, afebrile, those with previous antibiotic therapy and those without). However, correlations between DTPs of *Strepococcus spp.* or *Serratia spp.* and fever or DTPs of *Enterobacter spp.* or *H. influenzae* and previous antibiotic therapy were noticed (Table 5).

Table1: Frequency and differential time to positivity for bacteria isolated from patients with bloodstream infections

Bacteria	**N0 (%)**	**[1]DTP(h) Mean± SD(Min, Max)**
S. epidermidis	483 (49.0)	23.9±13.9 (1, 150)
S. aureus	83 (8.5)	18±19.6 (2, 166)
Acinetobacter spp.	75 (7.6)	25.7±11 (7, 52)
E. coli	45 (4.70)	13.5±7.3 (2, 36)
Enterococcus spp.	44 (4.6)	16.5±5.6 (6, 36)
Enterobacter spp.	34 (3.6)	13.4±5.5 (4.7, 30)
Diphtheroid like	24 (2.4)	37±24 (10, 86)
Bacillus spp.	23 (2.3)	17.5±12.7 (2, 55)
Kelbsiella spp.	22 (2.3)	11±3.4 (6, 20)
Pesudomonas spp.	18 (2.2)	13.7±6.7 (5, 28)
S. viridance	19 (2)	25±17.8 (10, 74)
Streptococcus spp.	15 (1.5)	17.5±9.9 (3, 36)
Serratia spp.	14 (1.4)	15±8.2 (5, 35)
Brucella spp.	13 (1.3)	65.5±32.7 (16, 131)
S. pneumoniae	10 (1.3)	14±4.5 (7, 20)
H. influenzae	11 (1.2)	21.7±14 (7, 61)
Oligella spp.	8 (0.8)	24±10.5 (10, 39)
Yeast	8 (0.8)	27.5±20.3 (10, 74)
C. davisae	7 (0.7)	32.6±23.3 (12, 80)
Micrococcus spp.	3 (0.6)	21±3.6 (18, 25)
Gr- Rod	4 (0.4)	24.7±13.6 (16, 45)
Salmonella spp.	3 (0.3)	8.7±4.7 (5, 14)
Citrobacter spp.	2 (0.2)	5.5±3.5 (3, 8)
Morganella spp.	2 (0.2)	32.5±20.5 (18, 47)
Edwardsiella spp.	1 (0.1)	5
Non Enterococcal	1 (0.1)	19
Peptoccus spp.	1 (0.1)	130
Total	985 (100)	

[1]Differential time to positivity

Table 2: Time to positivity (TTP) of *S. epidemidis* and its interpretation according to *Haimi-Cohen et al.* criteria (reference 8)

Number	**Percent**	**Time to positivity (h)**	**Interpretation**
100	20.7	≤15	True infection with 84% positive predictive value
209	43.3	15-22	Decision based on clinical evaluation
174	36	>22	Contamination with 87% positive predictive value

Discussion

Due to constant evolving antimicrobial resistant patterns which have resulted in present global public health problem, it is necessary to periodically monitor the antimicrobial sensitivity patterns in the region. This will help the clinicians embark on safe and effective empirical therapies, develop rational prescription programs and make policy decisions and finally assess the effectiveness of all.[1,2]

S. epidermidis is located on the top list of bacteria isolated from the blood samples. However, if an established cut off point for time to positivity (TTP) is considered, 76.3% of S. *epidermidis* isolates may be classified as skin contaminations.[8] Since *S. epidermidis* is the normal flora of the skin, such a high contamination incidence could be acceptable.[9] However, these results can be valuable if interpreted along with clinical signs and symptoms.[10] It has been suggested that the relationship of TTP with several clinical parameters in patients suffering from bacteremia could be predictive of the outcomes specially in life threatening conditions such as meningitis.[11-13] *S. aureus*, *Acinetobacter spp.*, *E. coli and Enterococcus spp.* were isolated with high frequencies from the blood samples. In literature, there are plenty of reports regarding antibiotics resistance in the above pathogens both internationally and regionally.[14-17] In addition, domestic reports on antibiotic resistance indicate vancomycin resistant entrococci (VRE), methicillin resistant *S. aureus* (MRSA), and multidrug resistant acinetobacter as the main nosocomial pathogens in Iran.[18-23] The existence of just a few effective antibiotics against Gram negative bacteria such as imipenem, amikacin and ciprofloxacin and vancomycin, co-amoxiclav and chloramphenicol for Gram positive bacteria gives rise to the need for a new strategy with emphasis on rational prescription of effective antibiotics. Furthermore, implementation of effective control measures is also necessary and helpful in alleviating the situation.

Fever is an important sign of infection in patients suffering from infectious diseases.[24] It is reasonable to expect lower DTPs in patients suffering from fever compared with afebrile counterparts due to the higher initial concentration of infective agents in their bloods.[25] However, data analysis did not find any significant statistical differences between DTPs of the bacteria isolated from febrile and afebrile patients. Nevertheless, a glance at DTPs of *Strepococcus spp.* or *Serratia spp.* and their relationships with fever indicates a weak association of these bacteria and corresponding DTPs (Table 5). Moreover, DTPs of *Enterobacter spp.* or *H. influenzae* in patients who previously received antibiotics were higher than those in patients not taking these drugs. These findings may point out a non-significant weak association of DTPs and the existence of fever or previous antibiotic consumption. If considered closely, the intensity of fever or duration of previous antibiotics treatment may significantly affect DTPs values.

Data analysis shows that penicillins and cephalosporins are not effective against the majority of Gram negative and positive bacteria. Acquisition of resistant determinant genes such as β-lactamase or cephalosporinase could be responsible for antibiotics resistance in bacteria isolated from blood samples.[26-29] Therefore, to treat the patients effectively, administration of these ineffective antibiotics should be ceased immediately. This could lower antibiotics pressure on sensitive strains and may reverse the situation.[30] Combination of vancomycin with imipenem can cover most Gram positive and negative bacteria whenever empirical therapy is indicated. Nevertheless, antibiotics such as co-amoxiclav with amikacin or chloramphenicol with ciprofloxacin could be alternative effective antibiotics if contraindication of the former (vancomycin with imipenem) poses.

Considering the above findings, we can conclude that the rational use of conventional effective antibiotics and periodic surveillance studies in order to monitor changes in bloodstream resistance patterns and implementation of preventive measures can alleviate the severity of the situation. Furthermore, combination of vancomycin with imipenem is recommended whenever empirical therapy needs to be considered.

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Conflict of interest: None declared.

Table 3: Susceptibility patterns of Gram negative bacteria isolated from patients with bloodstream infections to the tested antibiotics

Bacteria	Pat-tern	GM N0 (%)	KF N0 (%)	TS N0 (%)	CXM N0 (%)	CRO N0 (%)	CTX N0 (%)	IMI N0 (%)	CFX N0 (%)	CPM N0 (%)	AP N0 (%)	CAZ N0 (%)	AN N0 (%)	CIP N0 (%)	NOR N0 (%)	Total N0 (%)
Acinetobacter	S	35 (55)	18 (27)	37 (59)	11 (17)	19 (27)	24 (34)	52 (73)	5 (14)	8 (40)	4 (11)	40(66)	41(93)	65(89)	11(73)	370
spp.	R	29 (45)	48 (73)	22 (35)	54 (83)	49 (71)	47 (66)	19 (27)	30 (86)	10 (50)	31 (89)	19(31)	3(7)	8(11)	4(27)	(49.2)
N=75	IR	0	0	4 (6)	0	1 (2)	0	0	0	2 (10)	0	2(3)	0	0	0	373(49.6)
																9(1.2)
Brucella spp.	S	5 (100)	3 (37)	2 (33)	6 (75)	8 (89)	8 (89)	10 (100)			5 (100)	9(90)		9(100)		65 (82.3)
N=13	R	0	5 (63)	3 (50)	2 (25)	1 (11)	1 (11)	0	ND	ND	0	1(10)	ND	0	ND	13 (16.4)
	IR	0	0	1 (17)	0	0	0	0			0	0		0		1 (1.3)
E. coli	S	16 (35)	9 (22)	8 (21)	12 (35)	13 (30)	13 (31)	45 (100)		9 (75)	0	12(35)	14(61)	26(62)		177
N=46	R	30 (65)	32 (78)	30 (79)	22 (65)	30 (70)	29 (69)	0	ND	3 (25)	23 (100)	20(59)	9(39)	16(38)	ND	(41.8)
	IR	0	0	0	0	0	0	0		0	0	2(6)	0	0		244
																(57.8)
																2 (0.4)
Enterobacter	S	16 (48.5)	7 (23)	12 (40)	7 (28)	9 (30)	10 (31)	32 (100)		8 (73)	1 (7)	9(35)	12(60)	26(87)		149(47.5)
spp.	R	16 (48.5)	23 (74)	18 (60)	18 (72)	20 (67)	22 (69)	0	ND	3 (27)	13 (93)	15(58)	8(40)	4(13)	ND	160(50.9)
N=35	IR	1(3)	1 (3)	0	0	1(3)	0	0		0	0	2(7)	0	0		5(1.6)
H. influenzae	S	6 (67)	6 (67)	9 (82)	10 (91)	11 (92)	10 (91)	6 (100)		6 (86)	4 (44)	5(100)	3(100)	10(100)		86 (83.5)
N=12	R	3 (33)	1 (11)	2 (18)	1 (9)	1 (8)	1 (9)	0	ND	1 (14)	5 (56)	0	0	0	ND	15(14.5)
	IR	0	2 (22)	0	0	0	0	0		0	0	0	0	0		2 (2)
Kelbsiella	S	10 (50)	8 (36)	10 (45)	4 (21)	11 (48)	7 (30)	23 (100)			0	7(35)	7(78)	11(61)		98(48.7)
spp.	R	9 (45)	14 (64)	12 (55)	15 (79)	12 (52)	14 (61)	0	ND	ND	2 (100)	12(60)	1(11)	6(33)	ND	97(48.3)
N=23	IR	1 (5)	0	0	0	0	2 (9)	0			0	1(5)	1(11)	1(6)		6 ((3)
Pesudomo-	S	14 (74)	3 (27)	1 (7)	1 (9)	7 (39)	7 (39)	16 (77)		7 (70)	2 (20)	11(65)	16(94)	15(83)		100 (54)
nas spp.	R	5 (26)	8 (73)	14 (93)	10 (91)	10 (56)	10 (56)	3 (14)	ND	3 (30)	8 (80)	6(35)	1(6)	3(17)	ND	81(43.8)
N=22	IR	0	0	0	0	1(5)	1 (5)	2 (9)		0	0	0	0	0		4(2.2)
Serratia spp.	S	6 (60)	2 (15)	8 (57)	3 (25)	3 (25)	4 (33)	12 (92)			0	5(42)	11(100)	10(91)		64 (49.2)
N=14	R	4 (40)	11 (85)	6 (43)	9 (75)	9 (75)	8 (67)	1 (8)	ND	ND	10 (100)	6(50)	0	1(9)	ND	65(50)
	IR	0	0	0	0	0	0	0			0	1(8)	0	0		1 (0.8)
Total	S	108 (52.4)	56	87 (43.7)	54	81	83	196 (88.6)	5 (14.2)	38	51	98	104	172(81.5)	11	
	R	96 (46.6)	(27.9)	107 (53.7)	(29.2)	(37.5)	(38.1)	23 (10.5)	30	(63.4)	(47.3)	(52.9)	(81.8)	38 (18)	(73.3)	
	IR	2 (1)	142	5 (2.6)	131	132	132	2 (0.9)	(85.8)	20	57	79	22(17.4)	1 (0.5)	4 (26.7)	
			(70.6) 3		(70.8)	(61.1)	(60.5)		-	(33.3)	(52.7)	(42.8)	1 (0.8)		-	
			(1.5)			3 (1.4)	3 (1.4)			2 (3.3)	-	8(4.3)				

Abbreviations: GM; gentamicin, KF; cefalexin, TS; co-trimoxazole, CXM; cefuroxime, CRO; ceftriaxone, CTX; cefotaxime, IMI, imipenem, CFX; cefixime, CPM; cefepime, AP; ampicillin, CAZ; ceftazidime , AN; amikacin, CIP; ciprofloxacin, NOR; norfloxacin and ND; not determined.

Table 4: Susceptibility patterns of Gram positive bacteria isolated from patients bloodstream infections to the tested antibiotics tested

Bacteria	Pattern	GM N0 (%)	PG N0 (%)	V N0 (%)	KF N0 (%)	TS N0 (%)	OX N0 (%)	C N0 (%)	AMO N0 (%)	E N0 (%)	AP N0 (%)	T N0 (%)	CD N0 (%)	CIP N0 (%)	MET N0 (%)	T OB N0 (%)	AMC N0 (%)	KAN N0 (%)	Total N0 (%)
Enterococci spp.	S	10 (22)	4 (11)	38 (81)	12 (27)	14 (34)	4 (10)	30 (75)	1 (20)	5 (19)	4 (9)	3 (23)	11 (33)	16(53)	4(18)				156 (33.4)
N=48	R	34 (74)	25 (67)	9 (19)	32 (73)	26 (63)	36 (90)	9 (22.5)	4 (80)	21 (81)	29 (66)	9 (69)	21 (64)	11(37)	18(82)	ND	ND	ND	284 (60.6)
	IR	2 (4)	8 (22)	0	0	1 (3)	0	1 (2.5)	0	0	11 (25)	1 (8)	1 (3)	3(10)	0				28 (6)
S. aureus	S	64 (77)	7 (11)	80 (95)	61 (80)	61 (73)	47 (59)	68 (91)		34 (68)	9 (12)	11 (55)	41 (77)	43(88)	25(55.5)				551 (65.6)
N=84	R	18 (22)	58 (89)	4 (5)	15 (20)	22 (26)	32 (51)	5 (7)	ND	15 (30)	68 (88)	9 (45)	12 (23)	6(12)	20(44.5)	ND	ND	ND	284 (33.8)
	IR	1 (1)	0	0	0	1 (1)	0	2 (2)		1 (2)	0	0	0	0	0				5 (0.6)
S. epider-midis	S	288 (60)	42 (10)	476 (99)	343 (81.2)	210 (46)	147 (35)	340 (81)	29 (59)	87 (31)	64 (15)	65 (64)	187 (60.7)	207(68)	89(39)	21(62)	43(84)	17(59)	2655 (54.3)
N=483	R	188 (39)	360 (89.5)	6 (1)	77 (18.3)	244 (3)	273 (65)	77 (18)	19 (39)	190 (68)	348 (83)	37 (36)	120 (38.9)	95(31.3)	136(60)	13(38)	8(16)	12(41)	2203 (45.2)
	IR	4 (1)	2 (0.5)	0	1 (0.5)	3 (1)	0	3 (1)	1 (2)	1 (1)	5 (2)	0	1 (0.4)	1(0.5)	3(1)	0	0	0	25 (0.5
S. pneu-moniae	S	5 (42)	5 (50)	12 (100)	10 (91)	3 (33)	3 (30)	8 (89)		4 (57)	6 (54)		5 (83)	5(71.5)	3(60)				69 (63.4)
N=13	R	7 (58)	4 (40)	0	1 (9)	6 (67)	7 (70)	1 (11)	ND	3 (43)	4 (36)	ND	1 (17)	1(14.25)	2(40)	ND	ND	ND	37 (33.9)
	IR	0	1 (10)	0	0	0	0	0		0	1 (10)		0	1(14.25)	0				3 (2.7)
S. viridance	S	10 (48)	8 (50)	21 (96)	15 (94)	4 (23)	1 (6)	15 (88)		12 (75)	13 (82)	3 (60)	13 (100)	9(100)	5(45)				129 (66.2)
N=22	R	10 (48)	7 (44)	1 (4)	1 (6)	13 (77)	15 (94)	2 (12)	ND	2(12.5)	2 (12)	2(40)	0	0	6(55)	ND	ND	ND	61 (31.2)
	IR	1 (4)	1 (6)	0	0	0	0	0		2 (12.5)	1 (6)	0	0	0	0				5(2.6)
Total	S	377 (58.7)	66 (12.3)	627 (96.7)	441 (77.6)	292 (48)	363 (64.3)	461 (82.2)	30 (55.5)	142 (37.6)	96 (16.9)	82 (58.6)	257 (62.2)	280 (70.8)	126 (40.2)	21 (61.8)	43 (84.3)	17 (58.6)	
	R	257 (40.0)	454 (85.4)	20 (3.3)	125 (22)	311 (51.)	202 (35.7)	94 (16.8)	23 (42.6)	231 (61.3)	451 (79.8)	57 (40.7)	154 (37.3)	113(28.6)	182 (58.1)	13 (38.2)	8 (15.7)	12 (41.4)	
	IR	8 (1.3)	12 (2.3)		1 (0.4)	5 (1)		6 (1)	1 (1.9)	4 (1.1)	18 (32.3)	1 (0.7)	2 (0.5)	2 (0.6)	5(1.7)	-	-	-	

Abbreviations: GM; gentamicin, PG; penicillin G, V; vancomycin, KF; cefalexin, TS; co-trimoxazole, OX; oxacillin, C; chloramphenicol, AMO; amoxicillin, E; erythromycin, AP; ampicillin , T; tetracycline, CD; clindamycin, CIP; ciprofloxacin ,MET, methicillin TOB; tobramycin, AMC; co-amoxiclav and KAN; kanamycin

Table 5: Association between differential times to positivity of bacteria with febrile and previous antibiotic therapy of the patients suffering from bloodstream infections

Bacteria	Frequency (%)	Febrile Yes No	[1]DTP(h) Mean±SD	*P1*	[2]PAT Yes No	DTP(h) Mean±SD	*P2*
S. epidermidis	483 (49.0)	278 205	25±16 23±10	0.2	217 264	24±12 24±15	0.9
S. aureus	83 (8.5)	80 3	18±20 19±2	0.9	62 22	17±21 21±16	0.4
Acinetobacter spp.	75 (7.6)	38 37	25±11 27±11	0.6	59 16	24±12.5 27±9	0.2
Enterococcus spp.	44 (4.9)	38 8	17±6 15±3	0.3	32 12	17±6 16±4	0.7
E. coli	45 (4.70)	42 3	13±7 16±9	0.5	32 11	13±8 14±70	0.5
Enterobacter spp.	34 (3.6)	29 5	13±6 14±3	0.7	24 9	14±6 12±5	0.4
Diphtheroid like	24 (2.4)	18 6	41±26 24±9	0.1	7 17	33±25 39±24	0.6
Bacillus spp.	23 (2.3)	14 9	17±12 19±15	0.7	12 11	15±8 19±16	0.5
Kelbsiella spp.	22 (2.3)	22 0	11+3 NA	[2]NA	16 6	11±3 12±3	0.4
Pesudomonas spp.	18 (2.2)	17 1	14±7 13	0.8	16 2	14±7 12±0.7	0.8
S. viridance	19 (2)	14 5	24±17 30±21	0.5	12 6	18±7 31±21	0.2
Strepococcus spp.	15 (1.5)	10 4	16±9 22±11	0.3	3 11	10±7 19±10	0.1
Serratia spp.	14 (1.4)	13 1	15±8 20	0.5	11 3	15±9 17±3	0.7
Brucella spp.	13 (1.3)	13 0	NA NA	NA	9 4	66±25 63±50	0.9
S. pneumoniae	10 (1.3)	9 1	14±4 9	0.3	8 2	14±4 14±7	0.9
H. influenzae	11 (1.2)	9 2	21±15 23±3	0.9	5 6	25±21 19±4	0.5
Oligella spp.	8(0.8)	5 3	24±13 25±6	0.9	4 3	26±12 26±7	0.9
C. davisae	8 (0.8)	5 2	33±28 31±13	0.9	3 4	23±11 39±29	0.4
Micrococcus spp.	7 (0.7)	2 1	21±5 20	0.8	0 3	NA 21±4	NA
Gr- Rod	3 (0.6)	2 2	32+18 17+1	0.3	2 2	31±19 18±3	0.4
Salmonella spp.	4 (0.4)	3 0	9±5 NA	NA	1 2	14 6+1	0.1
Citrobacter spp.	3 (0.3)	1 1	8 3	NA	2 0	5.5±3.5 NA	NA
Morganella spp.	2 (0.2)	0 2	NA 35±20	NA	1 1	18 47	NA
Edwardsiella spp.	2 (0.2)	1 0	5 NA	NA	1 0	5 NA	NA
Non Entero-coccal	1 (0.1)	1 0	NA NA	NA	1 0	NA NA	NA
Peptoccus spp.	1 (0.1)	0 1	NA 13	NA	0 1	NA 13	NA

[1]Differential time to positivity; [2]previous antibiotic therapy; NA: not applicable.

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