Antibiotic resistance rates among bacterial isolates from infected patients of intensive care unit over the period (2011-2016) in Bursa, Turkey

Abstract

Background: The aims of this study were to evaluate the microbiological data for effective infection control and specific antimicrobial stewardship, and to report the epidemiology of intensive care unit (ICU)-acquired infections and the local antimicrobial resistance of pathogens

Methods: Data were collected between January 2011 and October 2016 from the cardiology and cardiovascular surgery patients. The identification and antimicrobial susceptibility analyses of clinical pathogenic isolates were determined by the automatic device system.

Results: *Klebsiella pneumoniae* was detected increasingly and significantly ($p=0.048$) resistant to imipenem (IMP). *Acinetobacter baumannii* was found increasingly and significantly ($p=0.045$, $p=0.030$, $p=0.006$, $p=0.027$) resistant to amikacin (AN), gentamicin (GN), trimethoprim-sulfamethoxazole (SXT) and tetracycline (TE), respectively. There was a significantly decrease in the resistant rates of IMP, piperacillin-tazobactam (TPZ), meropenem (MEM) and ciprofloxacin (CIP) for *Pseudomonas* spp. ($p=0.048$). All gram-negative bacteria isolates showed significantly increasing resistance rates to cefepime (CEP) ($p=0.015$). Also, all gram-positive bacteria demonstrated significantly decreasing resistance rates to teicoplanin (TEC) ($p=0.034$).

Conclusion: This study suggests that inadequacy of infection control measures such as hand hygiene and patient isolation may have contributed to increasing the rates of carbapenem-resistant *K. pneumoniae* (CR-KP) isolates in recent years.

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Introduction

The antimicrobial stewardship in intensive care unit (ICU) is highly important measurement to control antimicrobial resistance in most hospital. There are two main problems to this issue. Inappropriate usage of antibiotic therapy and poor concordance to the infection control policy. Both can lead to the occurrence of resistant pathogens by various molecular mechanisms such as mutation, gene transfer and selection of the resistant strains [1, 2]. Recently, most ICU-acquired infection are due to pathogens like methicillin-resistant *Staphylococci*, multidrug-resistant *Pseudomonas aeruginosa* and *Acinetobacter* species. Additionally, carbapenem resistant *K. pneumoniae* (CR-KP) are detected more frequently in the recent years worldwide [3-5]. Therefore, awareness about the current local epidemiology and antimicrobial susceptibility of bacterial isolates is an important factor in prescribing true empiric antibiotherapy in ICU [6, 7]. Despite this fact, medical treatment options of multidrug-resistant pathogens are limited [8].

The aim of this study is to report the epidemiology of ICU-acquired infections and the local antimicrobial resistance of microorganism isolates over a 6- year period.

Materials and Methods

Patients

Data were collected between January 2011-October 2016, retrospectively, from admitted adult cardiology and cardiovascular surgery (CVS) patients at Bursa Yuksek Ihtisas Training and Research Hospital, Turkey. This hospital is a tertiary care hospital serving a 3-million population region. ICU-acquired infections were diagnosed after 48 hours of ICU admission according to Centers for Disease Control and Prevention guidelines [9]. Piperacillin-tazobactam, imipenem, meropenem antibiotics were frequently used in treatment of ICU-acquired infection

caused by gram-negative bacteria and vancomycin, linezolid, daptomycin antibiotics were frequently used in treatment of ICU-acquired infection caused by gram-positive bacteria.

Microbiological analyses

Blood, urine, wound, sputum, tracheal aspirate and other clinical samples were collected from the patients who were prediagnosed with ICU-acquired infections. Cultivation of specimens were made and microbiological tests were used for identification of isolates. Bacterial isolates from blood cultures were detected using BACTEC 9240 (Becton Dickinson, USA). Identification and antimicrobial susceptibility analyses of pathogens were determined by the automatic device system (MicroScan Walkaway, Beckman Coulter, USA). The following antibiotics were used for gram-negative microorganisms; amikacin (AN), amoxicillin-clavulanate (AMC), gentamicin (GN), imipenem (IMP), piperacillin-tazobactam (TPZ), cefepime (CEP), cefotaxime (CTX), trimethoprim-sulfamethoxazole (SXT), meropenem (MEM), ciprofloxacin (CIP), ceftazidime (CAZ), levofloxacin (LEV), tetracycline (TE), cefazolin (CZ) antimicrobial resistance ratios were established. For gram-positive microorganisms; ampicillin (AM), ciprofloxacin (CIP), teicoplanin (TEC), tetracycline (TE), trimethoprim-sulfamethoxazole (SXT), vancomycin (VA), gentamicin (GN). All antimicrobial resistance ratios were determined according to the minimal inhibitor concentration (MIC) values of the current EUCAST criteria. Methicillin resistant *Staphylococcus* species was assessed according to ceftoxitin MIC values. *Candida* species was differentiated by APIc AUX kit (bioMérieux, France).

Statistical analyses

Data were analyzed by SPSS program version 21.0 with Fisher's exact chi-square test and Pearson chi-square test. Differences were accepted statistically significant at $p < 0.05$.

Results

The distribution of recovered pathogens in ICUs over a 6-year period is demonstrated in **Table 1**. *Acinetobacter baumannii* and coagulase-negative *Staphylococcus* (CNS) were the most common pathogens recovered. The distribution of resistance rates of recovered pathogens through three-year periods was determined. Antibiotic resistance rates of microorganisms between 2011-2012-2013 and 2014-

2015-2016 were combined and the total resistance rates in both periods were compared. A comparison between resistance rates in gram-negative pathogens during a 6-year period is demonstrated in **Table 2, 3**. A second comparison between resistance rates in gram-positive bacteria over a 6-year period is shown in **Table 4**.

Table 1. Distribution of ICU-acquired pathogens over the 6-year period (2011-2016).

Microorganism isolates	2011		2012		2013		2014		2015		2016	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
<i>Acinetobacter baumannii</i>	23	23.7	8	10	18	18.75	18	20.93	0		9	16.36
<i>Acinetobacter</i> spp.	2	2.1	10	12.5	7	7.29	10	11.62	16	21.33	6	10.90
<i>Candida albicans</i>	0		2	2.5	3	3.12	4	4.65	0		0	
<i>Candida</i> spp.	6	6.2	2	2.5	5	5.20	3	3.48	1	1.33	0	
<i>Citrobacter</i> spp.	1	1	0		2	2.08	0		1	1.33	2	3.63
<i>Enterococcus</i> spp.	0		4	5	3	3.12	2	2.32	0		2	3.63
<i>Enterobacter</i> spp.	1	1	2	2.5	0		0		1	1.33	0	
<i>Enterobacter aerogenes</i>	1	1	1	1.25	1	1.04	5	5.81	0		0	
<i>Enterobacter cloacae</i>	0		4	5	1	1.04	2	2.32	0		1	1.81
<i>Enterococcus faecalis</i>	5	5.2	2	2.5	8	8.33	4	4.65	3	4	4	7.27
<i>Enterococcus faecium</i>	3	3.1	0		3	3.12	1	1.16	1	1.33	1	1.81
<i>Escherichia coli</i>	11	11.3	5	6.25	6	6.25	3	3.48	10	13.33	5	9.09
Coagulase-negative staphylococci	8	8.3	17	21.25	18	18.75	9	10.46	12	16	9	16.36
<i>Klebsiella oxytoca</i>	0		1	1.25	0		0		0		0	
<i>Klebsiella pneumoniae</i>	8	8.2	3	3.75	2	2.08	8	9.30	3	4	5	9.09
<i>Klebsiella</i> spp.	0		3	3.75	0		2	2.32	6	8	0	
<i>Morganella morganii</i>	0		0		0		0		1	1.33	1	1.81
<i>Pseudomonas aeruginosa</i>	2	2.1	3	3.75	10	10.41	4	4.65	3	4	3	5.45
<i>Pseudomonas</i> spp.	0		0		2	2.08	3	3.48	2	2.66	0	
<i>Proteus mirabilis</i>	0		0		1	1.04	1	1.16	0		0	
<i>Providencia</i> spp.	1	1	0		0		0		0		0	
<i>Serratia marcescens</i>	6	6.2	0		2	2.08	0		1	1.33	1	1.81
<i>Staphylococcus aureus</i>	16	16.5	13	16.25	1	1.04	7	8.13	13	17.33	6	10.90
<i>Streptococcus pneumoniae</i>	1	1	0		1	1.04	0		1	1.33	0	
<i>Stenotrophomonas maltophilia</i>	1	1	0		2	2.08	0		0		0	
<i>Streptococcus</i> spp.	1	1	0		0		0		0		0	
Total	97	100	80	100	96	100	86	100	75	100	55	100

Table 2. Comparison of the antimicrobial resistance rates in different gram negative pathogens over two periods (2011-2013 versus 2014-2016).

Microorganism	Period	Amikacin		Amoxicillin/Clavulanate		Gentamicin		Imipenem		Piperacillin/Tazobactam		Cefepime		Cefotaxime	
		%	P*	%	p	%	p	%	p	%	p	%	p	%	p
Enterobacter cloacae	2011-2013	0.0		100.0		0.0		0.0		20.0	1.00	0.0	0.143	25.0	1.00
	2014-2016	0.0		100.0		0.0		0.0		0.0		66.7		33.3	
E. coli	2011-2013	9.1	0.642	93.3	0.314	47.6	0.180	0.0	0.450					37.5	1.00
	2014-2016	16.7		66.7		22.2		5.6						40.0	
Klebsiella pneumoniae	2011-2013	7.7	0.343	50.0	1.00	69.2	1.00	0.0	0.048	50.0	1.00			62.5	1.00
	2014-2016	25.0		50.0		62.5		31.2		50.0				50.0	
Klebsiella spp.	2011-2013					66.7	0.545	0.0						100.0	
	2014-2016					37.5		0.0						100.0	
Serratia marcescens	2011-2013	0.0		100.0		0.0		0.0				0.0		12.5	1.00
	2014-2016	0.0		100.0		0.0		0.0				0.0		0.0	
Pseudomonas aeruginosa	2011-2013	7.1	1.00			7.1	0.521	33.3	0.262	0.0					
	2014-2016	14.3				28.6		0.0		0.0					
Acinetobacter baumannii	2011-2013	83.0	0.045			67.6	0.030	97.8	1.00					100.0	
	2014-2016	100.0				92.6		96.3						100.0	
Acinetobacter spp.	2011-2013	33.3	0.184			78.9	0.222	76.5	0.721			94.7	1.00	94.7	1.00
	2014-2016	59.1				59.4		81.2				100.0		100.0	
Enterobacter aerogenes	2011-2013	0.0		100.0		0.0	0.464	0.0		0.0		0.0	0.196	0.0	
	2014-2016	0.0		100.0		40.0		0.0		0.0		60.0		0.0	
Citrobacter spp.	2011-2013	33.3	1.00			33.3	1.00	33.3	1.00						
	2014-2016	0.0				33.3		0.0							
Pseudomonas spp.	2011-2013							100.0	0.048	100.0	0.048				
	2014-2016							0.0		0.0					
Proteus mirabilis	2011-2013	0.0	1.00	0.0								0.0	1.00		
	2014-2016	100.0		0.0								100.0			
Gram Negative Microorganisms	2011-2013	37.5	0.190	92.9	0.057	50.0	0.620	47.1	0.902	36.0	0.569	53.8	0.015	75.4	1.00
	2014-2016	46.2		73.9		53.2		46.0		25.7		84.6		76.5	

*: p<0.05

Table 3. Comparison of antimicrobial resistance rates in different gram negative pathogens over two periods (2011-2013 versus 2014-2016).

Microorganism	Period	Trimethoprim/Sulfamethoxazole		Meropenem		Ciprofloxacin		Ceftazidim		Levofloxacin		Tetracycline		Cefazolin	
		%	P*	%	p	%	p	%	p	%	p	%	p	%	p
Enterobacter cloacae	2011-2013	20.0	1.00												
	2014-2016	0.0													
E. coli	2011-2013	76.5	1.00	0.0	0.450										
	2014-2016	80.0		5.6											
Klebsiella pneumoniae	2011-2013	61.5	0.714	0.0	0.096	61.5	0.673								
	2014-2016	68.8		30.8		50.0									
Klebsiella spp.	2011-2013	33.3	0.491			66.7	1.00								
	2014-2016	75.0				62.5									
Serratia marcescens	2011-2013			0.0				0.0	0.22						
	2014-2016			0.0				50.0							
Pseudomonas aeruginosa	2011-2013			33.3	0.345	20.0	1.00	46.7	0.68	0.0	1.00				
	2014-2016			10.0		25.0		60.0		16.7					
Acinetobacter baumannii	2011-2013	75.5	0.06	98.0	1.00	95.9	0.536	95.7	0.530	100.0		76.6	0.027		
	2014-2016	100.0		100.0		100.0		100.0		100.0		100.0			
Acinetobacter spp.	2011-2013			83.3	0.289	100.0		100.0		100.0					
	2014-2016			96.2		100.0		100.0		100.0					
Enterobacter aerogenes	2011-2013	0.0	0.196	0.0				0.0						100.0	
	2014-2016	60.0		0.0				0.0						100.0	
Citrobacter spp.	2011-2013	33.3	1.00			0.0									
	2014-2016	100.0				0.0									
Pseudomonas spp.	2011-2013			100.0	0.048	100.0	0.048								
	2014-2016			0.0		0.0									
Proteus mirabilis	2011-2013													0.0	
	2014-2016													0.0	
Gram Negative Microorganisms	2011-2013	64.3	0.123	52.2	0.791	75.5	0.386	76.3	0.11	88.1	0.757	78.0	0.055	100.0	0.381
	2014-2016	76.5		50.0		81.2		86.7		85.3		100.0		87.5	

*: p<0.05

Table 4. Comparison of antimicrobial susceptibility rates in different gram positive pathogens over two periods (2011-2013 versus 2014-2016).

Microorganism	Period	Ampicillin		Ciprofloxacin		Teicoplanin		Tetracycline		Trimethoprim/Sulfamethoxazole		Vancomycin		Gentamicin	
		%	P*	%	p	%	p	%	p	%	p	%	p	%	p
Staphylococcus aureus	2011-2013	100.0	0.248	75.0	0.111	0.0		53.3	0.693	33.3	0.290	0.0			
	2014-2016	81.2		38.5		0.0		42.9		15.4		0.0			
Enterococcus faecalis	2011-2013	0.0	0.169	25.0	0.315	10.0	0.476	70.0	0.659			0.0			
	2014-2016	18.2		62.5		0.0		54.5				0.0			
Enterococcus spp.	2011-2013	50.0	1.00					100.0				0.0			
	2014-2016	50.0						100.0				0.0			
CNS**	2011-2013	100.0	0.492			7.1	0.261	23.3	0.547	48.8	1.00	0.0		46.3	0.474
	2014-2016	93.1				0.0		33.3		52.4		0.0		56.7	
Enterococcus faecium	2011-2013	100.0				33.0	0.500					33.0	0.500		
	2014-2016	100.0				0.0						0.0			
Gram positive microorganisms	2011-2013	32.0	0.747	55.0	0.758	6.8	0.034	42.5	1.00	42.5	0.833	1.9	0.524	46.3	0.474
	2014-2016	37.5		47.6		0.0		43.9		38.2		0.0		56.7	

*: P<0.05; **: Coagulase-negative Staphylococcus.

Discussion

Hospitalization in ICU is an important risk factor to acquire infection with carbapenem resistant *K. pneumoniae* (CR-KP), because of usage of many invasive devices such as urinary catheters, central venous catheters, mechanical ventilation and the possibility of transmission infection between patients. Additionally, broad-spectrum antimicrobial drugs such as carbapenems are frequently used in ICUs and these drugs are known to contribute for emergence of CR-KP [10-12]. In our study,

K. pneumoniae was detected increasingly and significantly resistant to imipenem, because our tertiary care hospital admitted cardiology and cardiovascular surgery patients (CVS) from referral hospitals to our ICUs. We suspect that these patients have contributed for spread of CR-KP in our ICUs. In addition, the insufficient isolation of infected patients and inadequate ventilation in our ICUs have increased rates of infection and isolation of resistant pathogens among patients during the two compared periods (2014-2016 versus

2011-2013) as shown in **Table 2-4**. Also, similar increasing rates were observed in relation to use of urinary catheterization and the length period of usage it. Both these two factors were most probably increased infection with CR-KP in our intensive care units.

In our study, multidrug-resistant *A. baumannii* isolates were the most common cause of infections among our patients in ICUs as it has been recorded worldwide [13-16]. The increase in antibiotic resistance rates among *A. baumannii* isolates

was significant (**Table 2-3**). It has been reported that carbapenem-resistant *Acinetobacter* isolates can be increased rapidly and become a significant problem in intensive care unit patients. Additionally, rates of resistant *Acinetobacter* strains are observed to be higher in countries where carbapenems are intensely used [17, 18].

Studies have also shown an increasing carbapenem-resistance in *P. aeruginosa* isolates from ICU-acquired infections [19-21]. In our study, there was a significantly decrease in the resistant rates of *Pseudomonas* spp. and *P. aeruginosa* to IMP, TPZ, MEM and CIP, but both were not statistically significant. In addition, decreased rates of resistance to IMP and MEM were detected in all gram-negative pathogens and these were not statistically significant (**Table 2-3**). The reason for this decrease may be due the fact that in our hospital, our physicians used less empirical treatment in ICU-acquired infections and they are preferring to apply mostly treatment based on culture results. This approach may have led to reduce the occurrence of carbapenem-resistant pathogens in our hospital. It is also important to note that our hospital's microbiology laboratory provided 24-hour service, and offer a rapid assessment of positive blood cultures and the result of gram-staining.

In our hospital, physicians are preferring treatment of gram-positive bacterial infections with vancomycin, daptomycin and linezolid instead of teicoplanin. Despite this treatment approach, there was overall no change in rates of resistance among all gram-positive bacteria to these 3 drugs, but there was statistically significant decrease in resistance to TEC (**Table 4**). However, various studies have shown that teicoplanin could theoretically represent an acceptable alternative drug, since it has comparable efficacy compared to vancomycin in various disease conditions and excellent bone diffusion [22]. Extensive use of teicoplanin in ICU patients may result in development of increased resistance rates in gram-positive bacteria, whereas the usage of vancomycin occasionally during empirical therapy, and according

to MIC values were the main reasons for not increasing vancomycin resistance rates in gram-positive bacteria in this study [23-26].

In conclusion, this study shows that close cooperation between microbiology laboratory and physicians has been associated with decrease in carbapenem and vancomycin resistance rates in pathogens recovered from ICU's patients.

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Conflicts of interest

There are no conflicts of interest for this study.

Ethical approval

Not required.

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