Increased colistin resistance of *Acinetobacter* species in intensive care unit-acquired infections in a tertiary care hospital

Abstract

Background: The aim of our study was to evaluate the antimicrobial resistance rates among pathogen microorganisms especially colistin resistant rates of *Acinetobacter baumannii* in intensive care unit (ICU)-acquired infections and to determine infection-specific correct treatment strategies.

Methods: The data of adult and newborn infant patients diagnosed with ICU-acquired infection in a tertiary education and research hospital in Bursa in 2014 and 2016 were analyzed, retrospectively.

Results: *Acinetobacter baumannii* was the most frequent pathogen of ICU-acquired infections in 2014 and 2016. There was a significant increase in colistin (CO) resistance rates in *A. baumannii* (0.0%-6.8%). A significant increase in CO, cefepime (FEP), ciprofloxacin (CIP) resistance rates was established in all gram negative bacteria (0.0%-7.9%, 50.0%-91.9%, 54.7%-74.6%), respectively. A significant increase in the rate of detection of *A. baumannii* as the pathogen microorganism in respiratory tract infection (RTI) was established (53.9% -79.5%). In addition, the average ventilator-associated pneumonia (VIP) infection rate also increased in 2016 compared to 2014 (VIP rate 2014: 7.12, 2016: 7.45, per 1000 ventilator days). A significant decrease in the rate of detection of all gram negative microorganisms in the surgical site infection (SSI), and a significant increase in the rate of detection of all gram positive microorganisms in the SSI was determined.

Conclusion: Increased antimicrobial resistance, especially increased colistin resistance rates in ICU-acquired infections, necessitates the creation of new strategies in empirical therapy. Detection of antimicrobial resistance profiles of local and infectious pathogen microorganisms in ICUs is a good guide for correct antimicrobial management.

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Introduction

The frequent use of broad spectrum antibiotics in intensive care unit (ICU), leads to increased rates of antimicrobial resistance and more frequent occurrence of multidrug-resistant microorganisms [1-3]. Increased antimicrobial resistance in ICU-acquired pathogens complicates treatment and limits new treatment options [4-6]. Nowadays colistin is frequently used as an effective antibiotic in ICU-acquired infections caused by multiresistant gram-negative bacteria, but colistin resistance is also observed to be increasing in recent years [7-9]. In the management of antimicrobial resistance in ICUs; it is necessary to optimize specific diagnosis and treatment of infections. In addition, strategies for selection of antibiotics, optimization of dose and duration, prevention of the passage of resistant pathogenic microorganisms to the patient through correct infection control measures need to be developed [10]. Microbiologists, clinicians, and infection control staff must work together to identify specific common bacteria and antibiotic resistance profiles in ICUs to select the right antibiotics for treatment [4, 11].

The aim of this study was to evaluate the antimicrobial resistance rates especially colistin resistance rates of pathogen microorganisms in ICU-acquired infections and to determine infection-specific correct treatment strategies.

Materials and methods

Data collection

Bursa Yuksek Ihtisas Education and Research Hospital which is serviced 3 million population in Turkey, and is a tertiary care hospital with total of 147 ICU-patient beds including cardiovascular surgery (CVS), general surgery, internal medicine, cardiology, pediatrics, newborn and reanimation departments. In our study, the data of adult and newborn infants diagnosed with ICU-acquired infection in 2014 and

2016 were analyzed retrospectively. ICU-acquired infections were determined according to the criteria of Centers for Disease Control and Prevention (CDC) guidelines for patients after length of ICU stay of 48 hours. ICU-acquired infections were categorized according to CDC criteria as blood stream infection (BSI), respiratory tract infection (RTI), urinary tract infection (UTI), surgical site infection (SSI), skin and soft tissue infection (SSTI) and central nervous system infection (CNSI).

Microbiological tests

Bacterial and fungal cultivation were made from clinical samples (blood, cerebrospinal fluid, urine, wound, tissue, tracheal aspirate, etc.) of the ICU patients in microbiology laboratory. Positive blood and cerebrospinal fluid cultures were detected by automated blood culture system (BACTEC 9240 Blood Culture System; Becton Dickinson Biosciences). Identification and antibiograms of gram-positive and gram-negative bacteria and yeast fungi were determined from the pure isolates obtained from the cultures on the automated device (Vitek 2, bioMérieux, USA). All antibiotic resistance values were determined based on current EUCAST minimal inhibitor concentration (MIC) limit values. Amikacin (AN), ampicillin (AM), gentamicin (GN), imipenem (IMP), piperacillin-tazobactam (TPZ), FEP, cefotaxime (CTX), trimethoprim-sulfamethoxazole (SXT), meropenem (MEM), ceftazidim (CAZ), ceftriaxone (CRO), tetracycline (TE), ceftiofur (FOX), teicoplanin (TEC), vancomycin (VA), linezolid (LNZ) and colistin (CO).

Statistical analysis

The data were analyzed using the Fisher-exact Chi square test and the Pearson Chi square test by the SPSS program version 21.0. Statistically significant difference was accepted as $p < 0.05$ -95% and $p < 0.01$ -99%.

Results

The distribution of all pathogen microorganisms according to period of detection was shown in ICU-acquired infections (**Table 1**). *Acinetobacter baumannii* was the most frequent pathogen detected in ICU-acquired infections in 2014 and 2016, among gram-negative bacteria, whereas among gram-positive bacteria coagulase-negative *Staphylococcus* (CNS), and *Candida albicans* among *Candida* spp. was the most frequent isolates.

Antibiotic resistance rates of gram-negative pathogens in ICU-acquired infections were compared between 2014 and 2016 (**Table 2, 3**).

There was a significant increase in CO resistance rates in *A. baumannii* (0.0%-6.8%, $p < 0.05$). There was a significant increase in GN resistance rates in *Klebsiella pneumoniae* (41.9% -80.3%, $p < 0.01$). A significant decrease in TPZ resistance rates was found in *Pseudomonas aeruginosa* (65.1% - 31.4%, $p < 0.01$).

A significant increase in CO and FEP resistance rates was established in all gram negative bacteria (0.0%-7.9%, 50.0% -91.9%, $p < 0.01$). CIP resistance rates were also significantly increased (54.7% -74.6%, $p < 0.05$). The increase of AM, GN, CAZ, TPZ, IMP, MEM, and SXT resistance ratios were not statistically significant. The decrease in CTX and CRO resistance ratios was not statistically significant. AN resistance rate did not change.

Antibiotic resistance rates of gram-positive pathogens in ICU-acquired infections were compared between 2014 and 2016 (**Table 4**).

There was a significant decrease in GN resistance of CNS (76.0%-42.1%, $p < 0.05$) and a significant decrease in FOX resistance in *Staphylococcus aureus* (100.0% -75.0%, $p < 0.05$).

A significant decrease in FOX and GN resistance was determined in all gram positive bacteria (100.0% -75.0%, 76.0% -42.1%, $p < 0.05$). The decrease of LNZ, SXT, VA and TE resistance ratios was not statistically significant, and the increase of AM resistance was not statistically significant.

Table 1. Distribution of all recovered pathogens from ICU-acquired infections over the 2-year (2014 & 2016).

Microorganism	2014		2016	
	n	%	n	%
Gram Negative Bacteria				
<i>Acinetobacter baumannii</i>	89	26.0	73	25.4
<i>Acinetobacter</i> spp.	53	15.5	6	2.1
<i>Pseudomonas aeruginosa</i>	43	12.5	35	12.2
<i>Klebsiella pneumoniae</i>	31	9.0	69	24
<i>Escherichia coli</i>	13	3.8	23	8.0
<i>Enterobacter aerogenes</i>	6	1.8	1	0.3
<i>Pseudomonas</i> spp.	5	1.5	3	1.0
<i>Klebsiella</i> spp.	5	1.5	0	66.47
<i>Enterobacter</i> spp.	3	0.9	3	1.0
<i>Serratia marcescens</i>	3	0.9	2	0.7
<i>Enterobacter cloacae</i>	2	0.6	3	1.0
<i>Proteus mirabilis</i>	1	0.3	4	1.4
<i>Stenotrophomonas maltophilia</i>	1	0.3	1	0.3
<i>Citrobacter</i> spp.	0		2	0.7
<i>Burkholderia cepacia</i>	0		1	0.3
<i>Morganella morganii</i>	0		1	0.3
<i>Salmonella</i> spp.	0		1	0.3
<i>Klebsiella oxytoca</i>	0		0	
Other	0		0	
Gram Negative Bacterias				
Fermantatives	65	19	111	38.5
Non-Fermantatives	190	55.5	117	40.6
Total	255	74.6	228	79.2
Gram Positive Bacteria				
CNS	25	7.3	19	6.6
<i>Staphylococcus aureus</i>	19	5.5	12	4.3
<i>Enterococcus faecalis</i>	8	2.3	7	2.5
<i>Enterococcus faecium</i>	2	0.6	6	2.1
<i>Enterococcus</i> spp.	6	1.8	2	0.7
<i>Streptococcus pneumoniae</i>	1	0.3	0	
Gram Positive Bacterias	61	17.8	46	15.9
All Candida spesies				
<i>Candida</i> spp.	13	3.8	7	2.5
<i>Candida albicans</i>	9	2.6	3	1.0
<i>Candida glabrata</i>	0		1	0.3
<i>Candida parapsilosis</i>	3	0.9	2	0.7
<i>Candida tropicalis</i>	1	0.3	1	0.3
All Candida spesies	26	7.6	14	4.9
Total	342	100	288	100

Table 2. Comparison of antimicrobial resistance rates of gram negative pathogens in ICU-acquired infections over the 2-year (2014 & 2016).

Pathogens	Period	Amikacin		Ampicillin		Gentamicin		Imipenem		Piperacillin /Tazobactam		Cefepime		Cefotaxime	
		%	p	%	p	%	p	%	p	%	p	%	p	%	p
<i>E.coli</i>	2014	30.8	,727			38.5	1,00			61.5	1,00				
	2016	39.1				43.5				65.2					
<i>Klebsiella pneumoniae</i>	2014	35.5	,384			41.9	,000**			58.1	,160				
	2016	46.4				80.3				73.9					
<i>Pseudomonas aeruginosa</i>	2014	44.2	,350					48.8	,652	65.1	,006**				
	2016	31.4						42.9		31.4					
<i>Acinetobacter baumannii</i>	2014	62.9	1,00			69.7	,602								
	2016	63.0				74.0									
<i>Acinetobacter spp.</i>	2014					77.4	,440								
	2016					66.7									
<i>Pseudomonas spp.</i>	2014	40.0	1,00							40.0	1,00				
	2016	33.3								66.7					
All Gram Negative Bacterias	2014	48.2	1,00	94.1	1,00 ^a	62.3	,842	36.4	,395	56.4	,604	50.0	,000**	72.7	1,00
	2016	48.2		100,0		63.3		44.4		60.1		91.9		70.0	

*: p<0.05; **: p<0.01.

Table 3. Comparison of antibiotic resistance rates of gram-negative pathogens in ICU-acquired infections over the 2-year (2014 & 2016).

Pathogens	Period	Trimethoprim-sulfamethoxazole		Meropenem		Ciprofloxacin		Ceftazidime		Ceftriaxone		Colistin	
		%	p	%	p	%	p	%	p	%	p	%	p
<i>E.coli</i>	2014	69.2	,484 ^a					69.2	1,00 ^a	61.5	1,00		
	2016	52.2						65.2		65.2			
<i>Klebsiella pneumoniae</i>	2014	58.1	1,00 ^a					87.1	1,00 ^a	58.1	,160		
	2016	58.0						87.0		73.9			
<i>Pseudomonas aeruginosa</i>	2014					51.2	,108 ^a	62.8	,254 ^a	65.1	,006**		
	2016					31.4		48.6		31.4			
<i>Acinetobacter baumannii</i>	2014											0.0	,017 ^{a*}
	2016											6.8	
<i>Acinetobacter spp.</i>	2014												
	2016												
<i>Pseudomonas spp.</i>	2014					40.0	,196 ^a			40.0	1,00		
	2016					100.0				66.7			
All Gram Negative Bacterias	2014	56.9	,457 ^a	9.1	1,00 ^a	54.7	,013 ^{a*}	72.8	1,00 ^a	56.4	,604	0.0	,001 ^{a**}
	2016	62.9		17.9		74.6		73.3		60.1		7.9	

*: p<0.05; **: p<0.01.

Table 4. Comparison of antimicrobial resistance of gram-positive pathogens in ICU-acquired infections over the 2-year (2014 & 2016).

Pathogens	Period	Amikacin		Linezolid		Tetracycline		Trimethoprim / sulfamethoxazole		Vancomycin		Gentamicin		Cefoxitin	
		%	p	%	p	%	p	%	p	%	p	%	p	%	p
<i>Staphylococcus aureus</i>	2014							61.5	,717					100.0	,049*
	2016							65.2						75.0	
<i>Enterococcus faecalis</i>	2014	25.0	,608					58.1		50.0	,077				
	2016	42.9						73.9		0.0					
CNS	2014					36.0	1,00 ^a	65.1	,067	4.0	1,00	76.0	,031*		
	2016					36.8		31.4		0.0		42.1			
<i>Enterococcus faecium</i>	2014									0.0	,464				
	2016									50.0					
All Gram Positive Bacterias	2014	35.7	,128	2.4	1,00	43.4	,787 ^a		,064	10.0	1,00	76.0	,031*	100.0	,049*
	2016	69.2		0.0		36.8						42.1		75.0	

*: p<0.05; **: p<0.01.

The rates of ICU-acquired infections were compared in gram-negative pathogens between 2014 and 2016 (**Table 5**).

There was a significant decrease in the rate of detection of *A. baumannii* as the pathogen microorganism in BSI (40.4% -15.1%, p<0.01) and a significant increase in the rate of detection as the pathogen microorganism in RTI (53.9% -79.5%, p<0.01). A significant decrease in the rate of detection of *K.*

pneumoniae as the pathogen microorganism in UTI was detected (25.8% -8.7%, p <0.05).

The rate of detection of all gram-negative bacteria as pathogen microorganism in SSI were significantly decreased (3.1%-0.0%, p<0.01). The decrease of in the rate of detection as the pathogen microorganism in BSI and UTI and the increase in the rate of detection as an pathogen microorganism in RTI, SSTI and CNSI was not statistically significant.

Table 5. Comparison of ICU-acquired infection rates for gram negative pathogens during the 2-year (2014 & 2016).

Pathogens	Period	BSI		RTI		UTI		SSI		SSTI		CNSI	
		%	p	%	p	%	p	%	p	%	p	%	p
<i>E.coli</i>	2014	38.5	,475	7.7	,634	53.8	,310	0.0		0.0	,274	0.0	,508
	2016	26.1		17.4		34.8		0.0		17.4		8.3	
<i>Klebsiella pneumoniae</i>	2014	29.0	,191	41.9	1,00	25.8	,031*	3.2	,310	0.0	,568	0.0	,568
	2016	43.5		42.0		8.7		0.0		2.9		2.9	
<i>Pseudomonas aeruginosa</i>	2014	16.3	,538	60.5	,230	14.0	,119			7.0	,696	2.3	1,00
	2016	11.1		75.0		2.8				11.1		0.0	
<i>Acinetobacter baumannii</i>	2014	40.4	,000**	53.9	001**	2.2	1,00	2.2	,502	1.1	1,00	0.0	,202
	2016	15.1		79.5		2.7		0.0		0.0		2.7	
All Gram Negative Bacterias	2014	32.9	,432	50.6	,201	10.2	,643	3.1	,008**	3.1	,261	0.4	,058
	2016	29.4		56.6		8.8		0.0		5.3		2.6	

*: p<0.05; **: p<0.01.

Table 6. Comparison of ICU-acquired infection rates in gram-positive and *Candida* microorganisms during the 2-year (2014 & 2016).

Microorganisms	Period	BSI		RTI		UTI		SSI	
		%	p	%	p	%	p	%	p
<i>Staphylococcus aureus</i>	2014	78.9	,253	21.1	,676			0.0	,387
	2016	58.3		33.3				8.3	
<i>Enterococcus faecalis</i>	2014	50.0	1,00			50.0	1,00		
	2016	57.1				42.9			
CNS	2014	100.0	,444a			0.0	1,00	0.0	,444
	2016	95.0				0.0		5.0	
<i>Enterococcus faecium</i>	2014	100.0	1,00a			0.0	1,00		
	2016	83.3				16.7			
All Gram Positive Bacterias	2014	80.3	,487	8.2	1,00	11.5	,754	0.0	,032*
	2016	73.9		8.7		8.7		8.7	
<i>Candida spp.</i>	2014	50.0	1,00			50.0	1,00		
	2016	57.1				42.9			
<i>Candida albicans</i>	2014	66.7	,509			33.3	,509		
	2016	100.0				0.0			
All <i>Candida</i> species	2014	60.0	,514			40.0	,514		
	2016	71.4				28.6			

*: p<0.05

The distribution of ICU-acquired infection rates in gram-positive and fungal pathogens were shown between the years 2014 and 2016 (**Table 6**).

A significant increase in the rate of detection of all gram positive bacteria as the pathogen microorganism in SSI was found (0.0%-8.7%, p<0.05). The increase of in the rate of detection as a pathogen microorganism in RTI and the decrease of in the rate of detection as a pathogen microorganism in BSI and UTI was not statistically significant.

A non-significant increase in BSI and a non-significant decrease in UTI were detected in the rates of all *Candida* species and *Candida albicans*.

Discussion

Routine surveillance and reporting on prevalence of infection and antimicrobial resistance patterns of isolates among patients in ICUs are essential

measurements to control misuse of certain anti-microbial drugs and to reduce emergence of more resistant pathogens. Colistin resistance rates ranging from 0.9% to 40.7% have been reported between 2001 and 2011, in many countries of Asia, Europe and the United States [12, 13]. According to this study, there was a significant increase in colistin resistance rates among *A. baumannii* and all gram-negative bacteria isolates (p<0.05, p<0.01) (**Table 3**). First, the rates of colistin resistance reported in *A. baumannii* were 5.9% in 1999 in the Czech Republic. According to studies from Turkey, colistin resistance rates were reported to be ranged between 0% in 2014 and 0.6% in 2016 [14, 15]. The primary cause of increased colistin resistance rates in our study was the significant especially for CIP, FEP, IMP, MEM, and TPZ which were frequently used in treatment of ICU-acquired infections caused by gram-negative pathogens (**Table 2, 3**).

In our hospital, many antibiotics including carbapenems are becoming useless in the treatment of multidrug resistant ICU-acquired *A. baumannii* infections. For this reason, colistin has been started to be used in empirical treatment. However, a recently increase in colistin resistance to already exist multi-resistant gram-negative causing infections further complicates the selection of already limited treatment options. Studies from different countries have shown that increasing CIP, TPZ, and carbapenem resistant in gram-negative bacteria isolates from intensive care units, as well as the increasing of community antimicrobial resistance rates, have affected empirical treatment choice [16, 17]. Common alternative antimicrobial treatment strategies need to be developed where the use of colistin should be limited for empirical treatment of patients of intensive care units as has been done in our hospital.

The increase in the detection rate of *A. baumannii* as a pathogen causing RTIs was found significant compared to other gram-negative pathogens ($p < 0.01$) (**Table 5**). The average ventilator-associated pneumonia (VIP) infection rate also increased in 2016 compared to 2014 (VIP rate 2014: 7.12, 2016: 7.45 per 1000 ventilator days). The efficacy of colistin treatment was noticed clearly in multidrug resistant *A. baumannii* pneumonias, especially among patients in ICU-acquired infections. Several studies have recommended a combined treatment with colistin [18, 19]. In our hospital, the detection of multi-resistant *A. baumannii* in ICU-acquired infections resulted in increasing the use of colistin and consequently a significant increase in colistin resistance was detected. Increasing infection control measures by improving isolation conditions, especially in our patients with RTIs, which were frequently infected with multi-drug resistant *A. baumannii*, may lead to a decrease in colistin resistance rates as has been demonstrated by other studies [20, 21]. In addition, we found a significant decrease in the rate of

detection of all gram negative and gram positive bacteria as pathogens in BSI and UTI (**Table 5, 6**). When invasive device associated infections in ICU were examined, central venous catheter-related bloodstream infection rate (2.98%/2014 versus 2.97%/2016:) and catheter-related urinary tract infection rate (0.97%/2014 versus 0.61%/2016) were also found to be slightly decreased in our hospital. Several studies have found that The incidence of ICU-acquired infections, the distribution of pathogens and antibiotic resistance, and the frequency of infection from invasive devices are interrelated and should be analysed together [22, 23]. Therefore, a decrease in using invasive devices can reduce the frequency of acquired multidrug resistant bacteria [23].

This study demonstrated that gram-negative pathogens were more common in ICU-acquired infections in 2016 than 2014 (**Table 1**). In addition, a significant decrease in the rate of detection of all gram-negative bacteria isolates in the SSI ($p < 0.01$), and also a significant increase in the rates of all gram positive bacteria in the SSI ($p < 0.05$) was observed (**Table 5**). The reason for the increase of SSI caused by gram-positive pathogens is related to patients who were admitted to the CVS and gynecology ICUs. Therefore, it is also important to choose empiric antibiotherapy which are effective against gram-positive.

Conclusion

In conclusion, increased antimicrobial resistance, especially increased colistin resistance rates in ICU-infected patients, necessitates the creation of new strategies in empirical therapy. Reporting of antimicrobial resistance profiles of recovered pathogens in ICUs is recommended guide for correct antimicrobial management and control nosocomial infection.

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Conflicts of interest

There are no conflicts of interest for this study.

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