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Antibacterial resistance patterns and incidence of hospital-acquired *Staphylococcus aureus* bacteremia in a tertiary care educational hospital in Turkey: a perspective from 2001 to 2013*

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Background/aim: *Staphylococcus aureus* is an important nosocomial pathogen and a successful antimicrobial-resistance developer. In this study we retrospectively evaluated the resistance patterns and incidence of microbiologically confirmed nosocomial bacteremia (MCNB) related *S. aureus* strains between 2001 and 2013.

Materials and methods: Any patient in whom *S. aureus* was isolated in at least one set of blood cultures (sent to the bacteriology laboratory 72 h after hospital admission) was considered to have MCNB.

Results: The methicillin-resistant *S. aureus* (MRSA) rate in 2001 was 73.8% whereas it was 36.2% in 2013. When the 2001–2003 and 2011–2013 periods were compared, resistance to oxacillin, levofloxacin, gentamicin, erythromycin, and clindamycin decreased significantly ($P < 0.05$). When we evaluated the total *S. aureus*, MRSA, and methicillin-sensitive *S. aureus* (MSSA) bacteremia rates per 1000 days and 1000 patients, there was an increase in the 2004–2005 period, which was followed by a slight decrease until 2013 ($P < 0.05$). There was a plateau in MCNB-related *S. aureus* rates between 2008 and 2011.

Conclusion: There was a decrease in overall *S. aureus* and MRSA bacteremia incidence as well as MRSA rates except for a plateau between 2008 and 2011. This steady decrease in the resistance rates is most probably due to the 2003 budget application and application of antimicrobial stewardship.

Key words: Antimicrobial resistance epidemiology, bacteremia, *Staphylococcus aureus*, MRSA, infectious diseases, erythromycin, glycopeptides, vancomycin, teicoplanin, incidence

1. Introduction

Staphylococcus aureus is a globally important cause of healthcare-associated infections. Moreover, it is a very successful antimicrobial-resistance developer (1). Methicillin-resistant *S. aureus* is an important nosocomial pathogen in Turkey and many other countries (1,2). Nosocomial methicillin-resistant *S. aureus* (MRSA) infection rates differ according to countries, regions, and hospitals (1–4). Ten, 50, and 90 percentile methicillin-resistance rate in *S. aureus* strains causing healthcare-associated infections in Turkish tertiary-care university hospitals were 8.05%, 43.24%, and 78.26% in 2012, respectively. The overall cumulative MRSA rate in the 373 hospitals was 53.88% (1672/3103) (5). Periodical control of resistance rates in major nosocomial pathogens is important in the selection of empirical therapy regimens. In the present study it was aimed to evaluate the resistance patterns and incidence of microbiologically confirmed nosocomial bacteremia (MCNB)-related *S. aureus* strains between 2001 and 2013 retrospectively.

2. Materials and methods

Any patient in whom *S. aureus* was isolated in at least one set of blood cultures (sent to the bacteriology laboratory 72 h after hospital admission) was considered to have MCNB. Data of antibacterial resistance and hospital admission duration were extracted from the hospital database. Double or more isolates during each episode

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were counted as one episode. Resistance patterns in the 2001–2003 and 2011–2013 periods were compared by chi-square test. Blood cultures were performed on Bact/Alert (bioMérieux, Durham, NC, USA). Bacterial identification was performed by using automated API (bioMérieux). Oxoid antibiotic discs (oxacillin 1 μg, gentamicin 30 μg, levofloxacin 5 μg, erythromycin 15 μg, clindamycin 15 μg, penicillin 10 μg, England) were used to test antibacterial susceptibility via disc diffusion method by following the recommendations of the Clinical and Laboratory Standards Institute (6).

In addition, the data related to the number of overall inpatients and the total patient days for each year between 2001 and 2013 were retrieved from the hospital database. By using these data, we calculated the nosocomial *S. aureus*/MRSA and MSSA bacteremia incidence for every 1000 patient days and 1000 patients per year. The chi-square test was used for the statistical analysis of susceptibility data.

3. Results

The MRSA rate in 2001 was 73.8% whereas it was 36.2% in 2013. There was a steady decrease between 2003 (76.7%) and 2005 (55.3%), a plateau (ranging between 58.8% and 63.3%) between 2006 and 2009, and a decrease after 2009 through 2013 (63.3%–36.2%). When the 2001–2003 and 2011–2013 periods were compared, resistance to oxacillin, levofloxacin, gentamicin, erythromycin, and clindamycin decreased significantly (Table 1; $P < 0.05$). When we evaluated the total *S. aureus*, MRSA, and MSSA bacteremia rates per 1000 days and 1000 patients, there was an increase in the 2004–2005 period, which was followed by a slight decrease until 2013 (Table 2; Figures 1 and 2). When we compared the 2001–2003 period with the 2011–2013 period, overall *S. aureus*, MRSA, and MSSA bacteremia rates decreased significantly (Table 2; $P < 0.05$).

4. Discussion

Antibiotic stewardship, education of hospital staff, effective utilization of microbiology laboratory, and seek and destroy policy as well as isolation of infected cases, hand hygiene, and limited in-hospital transfer of MRSA cases are among the most important measures for MRSA prevention (7). Recent Infectious Diseases Society of America guidelines suggest preauthorization and/or prospective audit and feedback over no such interventions (strong recommendation, moderate-quality evidence) (8). Compatible with these suggestions, in 2003, the Turkish Ministry of Finance, which is responsible for reimbursement of over 90% of the Turkish population's health expenditures, released a new budget application instruction for regulating the usage of parenteral antibiotics inside and outside of the hospitals. According to this instruction, the reimbursement of parenteral vancomycin, teicoplanin, meropenem, imipenem, piperacillin/tazobactam, and ticarcillin/clavulanate is restricted without prior approval from an Infectious Diseases Specialist (IDS). Reimbursement of ceftriaxone, cefotaxime, ceftizoxime, cefoperazone, ceftazidime, cefoperazone/sulbactam, cefepime, ciprofloxacin, levofloxacin, netilmicin, amikacin, and isepamicin is unlimited, when prescribed for the first 72 h of the treatment, for all specialists (except general practitioners) but further usage required IDS approval. The other antimicrobials are reimbursed without any restriction by prescription of any medical doctor (1,9). Decrease in cost and changes in antimicrobial resistance are known results of antibiotic restriction policies (1,9–11). The intervention resulted in decreased use of third generation cephalosporins and quinolones (1,9). Decreases in overall antibiotic consumption as well as cephalosporins and quinolones are associated with decreases in MRSA incidence and MRSA rates (1,9). Although the hand hygiene compliance rate was traditionally not high (12), our Nosocomial Infection Control Committee is working hard on the issue and the hand hygiene compliance rates increased to higher levels (29% in 2014 July–September period, unpublished data). The infection control committee does not implement routine contact isolation for MRSA but vancomycin-resistant enterococci and colistin-resistant *Acinetobacter* and *Pseudomonas* as well as carbapenem-resistant Enterobacteriaceae. A seek and destroy policy around the hospital was not implemented except in neurosurgery (since 2008 July) during the study period (13). During the 13 years there were several epidemics due to VRE and carbapenem-resistant Enterobacteriaceae, which are on the rise in other parts of Turkey in recent years. Universal isolation precautions were implemented for management of these epidemics. Several interventional programs are planned for improving the situation. Personnel screening is not implemented routinely except for VRE epidemics. A self-decrease (by the increase in *Acinetobacter* infections) or a subtle effect of the prevention methods during these epidemics cannot be excluded. However, in our opinion, the most probable reason for the MRSA rate decrease until 2005 is the effect of antimicrobial stewardship efforts, which resulted in decreased third generation cephalosporin and quinolone consumption. We may speculate that the plateau period of MRSA rates after that year may be due to the limitations of the antibiotic stewardship alone. In addition, the increase in the patient number and patient days with the start of the hospital service to all people covered by general social security (until that year only state employees could come to the hospital directly/without any referral) might have contributed to the situation. The increase in the general incidence during a simultaneous decrease in MRSA rates through 2004–2005 might have been due to the higher

Table 1. Distribution of the resistance patterns of the nosocomial bacteremia associated *S. aureus* strains from 2001 to 2013.

		Year															
		2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2001.2003	2011.2013	P value∞
Methicillin	Total N	252	177	116	188	208	211	202	162	139	109	112	93	47	545	252	
	Resistant	73.8%	70.1%	76.7%	63.3%	55.3%	58.8%	56.9%	60.5%	63.3%	60.6%	57.1%	44.1%	36.2%	73.2%	48.4%	
	Resistant N	186	124	89	119	115	124	115	98	88	66	64	41	17	399	122	P < 0.001
	R-CPTP*	3.62%	2.33%	1.62%	2.15%	2.05%	1.93%	1.76%	1.53%	1.64%	1.23%	1.20%	0.73%	0.28%	2.50%	0.09%	
	R-CPTDOHʊ	0.41%	0.25%	0.19%	0.25%	0.23%	0.23%	0.21%	0.20%	0.19%	0.14%	0.14%	0.09%	0.04%	0.28%	0.07%	
Levofloxacin	Total N	155	122	116	172	206	198	143	157	134	87	105	88	41	393	234	
	Resistant	76.1%	76.2%	57.8%	57.6%	51.5%	50.0%	44.8%	63.1%	60.4%	59.8%	52.4%	43.2%	24.4%	70.7%	44.0%	
	Resistant N	118	93	67	99	106	99	64	99	81	52	55	38	10	278	103	P < 0.001
	R-CPTP	2.29%	1.75%	1.22%	1.79%	1.89%	1.54%	0.98%	1.54%	1.51%	0.97%	1.02%	0.68%	0.16%	1.74%	0.60%	
	R-CPTDOH	0.26%	0.19%	0.14%	0.21%	0.22%	0.18%	0.12%	0.20%	0.17%	0.11%	0.12%	0.08%	0.02%	0.20%	0.07%	
Gentamicin	Total N	249	177	116	188	208	209	200	161	138	109	112	92	47	542	251	
	Resistant	61.4%	61.0%	69.0%	54.3%	48.1%	56.5%	53.0%	59.6%	55.8%	57.8%	50.9%	33.7%	25.5%	62.9%	39.8%	
	Resistant N	153	108	80	102	100	118	106	96	77	63	57	31	12	341	100	P < 0.001
	R-CPTP	2.97%	2.03%	1.45%	1.84%	1.79%	1.83%	1.62%	1.50%	1.44%	1.17%	1.06%	0.56%	0.20%	2.14%	0.59%	
	R-CPTDOH	0.34%	0.22%	0.17%	0.21%	0.20%	0.21%	0.19%	0.20%	0.16%	0.07%	0.12%	0.07%	0.03%	0.24%	0.07%	
Erythromycin	Total N	251	177	116	188	208	198	185	158	138	108	107	93	47	544	247	
	Resistant	66.9%	61.0%	62.9%	48.4%	33.7%	50.5%	37.3%	48.1%	57.2%	29.6%	29.9%	39.8%	27.7%	64.2%	33.2%	
	Resistant N	168	108	73	91	70	100	69	76	79	32	32	37	13	349	82	P < 0.001
	R-CPTP	3.26%	2.03%	1.33%	1.64	1.25%	1.55%	1.05%	1.19%	1.47%	0.60%	0.60%	0.66%	0.21%	2.19%	0.48%	
	R-CPTDOH	0.37%	0.22%	0.15%	0.19	0.14%	0.18%	0.13%	0.16%	0.17%	0.07	0.07	0.08	0.03	0.25	378.588	
Clindamycin	Total N	251	177	116	187	208	198	189	160	135	108	109	92	47	544	248	
	Resistant	43.4%	36.7%	50.9%	38.0%	28.8%	38.4%	21.7%	26.9%	33.3%	23.1%	20.2%	29.3%	17.0%	42.8%	23.0%	
	Resistant N	109	65	59	71	60	76	41	43	45	25	22	27	8	233	57	P < 0.001
	R-CPTP	2.11%	1.22%	1.07%	1.28%	1.07%	1.18%	0.63%	0.67%	0.84%	0.47%	0.41%	0.48%	0.13%	1.46%	0.33%	
	R-CPTDOH	0.24%	0.13%	0.12%	0.15%	0.12%	0.14%	0.07%	0.09%	0.10%	0.05%	0.05%	0.06%	0.02%	0.17%	0.04%	
Penicillin	Total N	251	177	116	188	208	211	202	162	139	109	112	93	47	544	252	
	Resistant	92.8%	93.2%	96.6%	93.1%	92.3%	92.4%	93.1%	93.8%	91.4%	90.8%	93.8%	89.2%	78.7%	93.8%	89.3%	
	Resistant N	233	165	112	175	192	195	188	152	127	99	105	83	37	510	225	P = 0.028
	R-CPTP	4.52%	3.10%	2.03%	3.16%	3.43%	3.03%	2.87%	2.38%	2.37%	1.85%	1.96%	1.49%	0.61%	3.20%	1.32%	
	R-CPTDOH	0.51%	0.34%	0.23%	0.37%	0.39%	0.36%	0.34%	0.31%	0.27%	0.22%	0.23%	0.18%	0.08%	0.36%	0.16%	
Total patients per year		51,444	53,178	54,997	55,347	55,860	64,322	65,381	63,899	53,610	53,542	53,670	55,685	60,970	159,619	170,325	
Total days of hospitalization per year		454,626	488,513	479,664	475,966	491,450	546,449	550,894	486,612	467,355	458,169	463,683	454,250	460,655	1,422,803	1,378,588	

∞Analyis between 2001–2003 and 2011–2013
*R-CPTP = Resistant cases per thousand patients
ʊR-CPTDOH = Resistant cases per thousand days of hospitalization

requests for infectious diseases consultation, resulting in more requests for blood cultures. The second downward trend is probably mostly due to the introduction of nonglycopeptide antibiotics such as linezolid, daptomycin, tigecycline, and colistin for both gram-positive and gram-negative bacteria, which decreased the overall glycopeptide and beta-lactam consumption. Hence, the lower antibiotic pressure might have contributed to the decrease in the resistance (1).

Our study has several limitations. The study is based on retrospective data. In addition, it is possible that all patients with fever might have not been subjected to blood culture during the study period. Hence, all the presented data represent the overall MCNB but may not represent all the *S. aureus* bacteremia episodes. We did not evaluate the treatment regimens as well as outcomes of the MCNB. Despite these disadvantages, to the best of our knowledge this is the largest and the most comprehensive set of data regarding MCNB *S. aureus* and its incidence in Turkey.

According to results of this retrospective perspective of 13 years, there was a steady decrease in MRSA rates between 2003 and 2005 followed by a plateau between 2006 and 2009, and a decrease from 2009 through 2013. MRSA and MSSA bacteremia rates per 1000 days and 1000 patients increased in the 2004–2005 period, which was followed by a slight decrease until 2013. This steady

Table 2. Healthcare-associated *S. aureus*/methicillin-resistant *S. aureus* and methicillin-sensitive *S. aureus* bacteremia incidence per 1000 patients and 1000 patient days from 2001 to 2013.

	Year														
	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2001.2003	2011.2013
MRSA (N)*	186	124	89	119	115	124	115	98	88	66	64	41	17	399	122
MRSA percent	73.8	70.1	76.7	63.3	55.3	58.8	56.9	60.5	63.3	60.6	57.1	44.1	36.2	73.2	48.4
MRSA-PTP[o]	3.62	2.33	1.62	2.15	2.05	1.93	1.76	1.53	1.64	1.23	1.20	0.73	0.28	2.50	0.09
MRSA-PTDOH [ʍ]	0.41	0.25	0.19	0.25	0.23	0.23	0.21	0.20	0.19	0.14	0.14	0.09	0.04	0.28	0.07
MSSA (N)[ц]	66	53	27	69	93	87	87	64	51	43	48	52	30	146	130
MSSA percent	26.2	29.9	23.3	36.7	44.7	41.2	43.1	39.5	36.7	39.4	42.9	55.9	63.8	26.8	51.6
MSSA-PTP	1.28	0.99	0.49	1.25	1.66	1.35	1.33	1.0	0.95	0.8	0.89	0.93	0.49	0.91	0.76
MSSA-PTDOH	0.14	0.11	0.06	0.14	0.19	0.16	0.16	0.13	0.11	0.09	0.10	0.11	0.07	0.10	0.09
Total-SA (N)[я]	252	177	116	188	208	211	202	162	139	109	112	93	47	545	252
Total-SA-PTP	4.90	3.33	2.10	3.40	3.72	3.28	3.09	2.54	2.59	2.03	2.08	1.67	0.77	3.41	1.48
Total-SA- PTDOH	0.55	0.36	0.24	0.39	0.42	0.39	0.37	0.33	0.30	0.24	0.24	0.20	0.10	0.38	0.18
Total patients per year	51,444	53,178	54,997	55,347	55,860	64,322	65,381	63,899	53,610	53,542	53,670	55,685	60,970	159,619	170,325
Total days of hospitalization per year	454,626	488,513	479,664	475,966	491,450	546,449	550,894	486,612	467,355	458,169	463,683	454,250	460,655	1,422,803	1,378,588

* MRSA: Methicillin-resistant *Staphylococcus aureus*
[o] -PTP: Per thousand patients
[ʍ] -PTDOH: Per thousand days of hospitalization
[ц] MSSA: Methicillin-sensitive *Staphylococcus aureus*
[я] Total SA: Total healthcare-associated bacteremia *Staphylococcus aureus* isolates

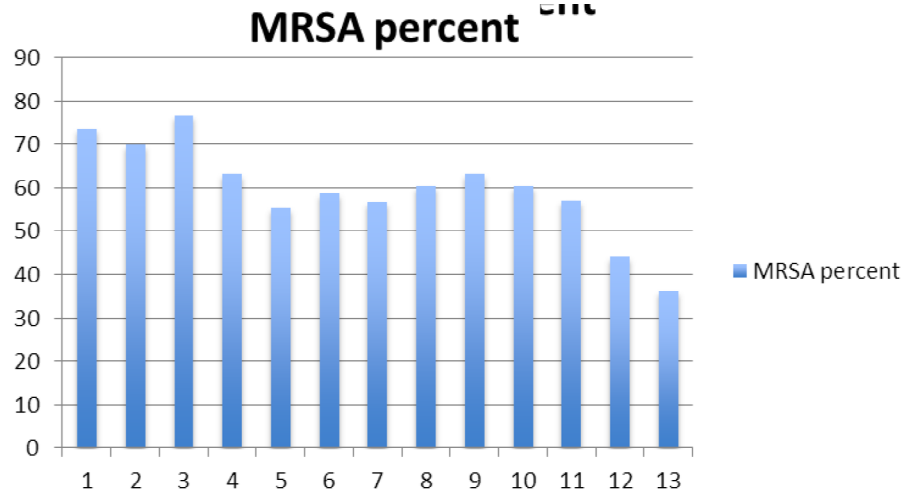

Figure 1. Change in MRSA rates in microbiologically confirmed nosocomial bacteremia related *S. aureus* strains between 2001 and 2013.

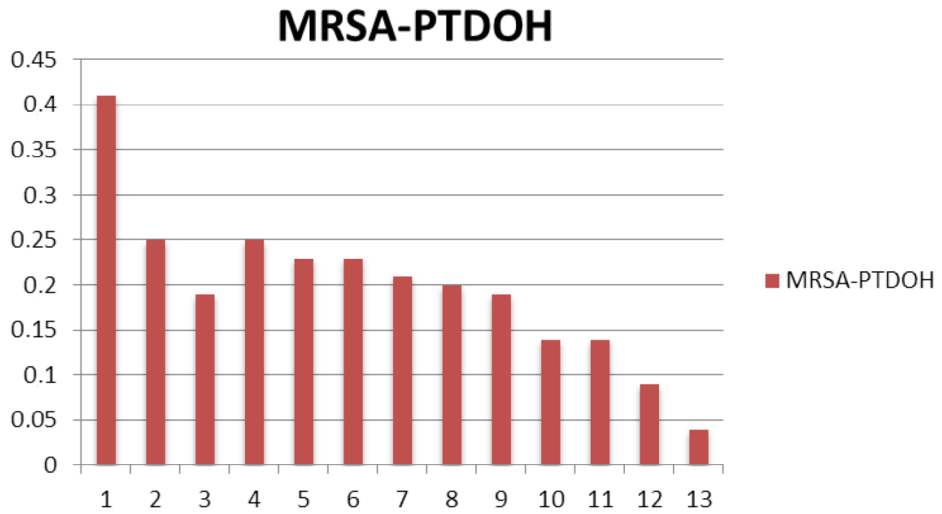

Figure 2. Change in incidence of microbiologically confirmed nosocomial bacteremia related *S. aureus* strains between 2001 and 2013 (as per 1000 patient days).

decrease in the resistance rates is most probably due to the positive effects of the 2003 budget application, antimicrobial stewardship efforts, and introduction of newer antibiotics to the market.

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