1-1-2013

Invasive device-associated hospital infection rates, etiological agents, and their antibiotic susceptibilities in the medical intensive care unit of a university hospital in Turkey

SALİHA ÇEVİK

VUSLAT BOŞNAK

MUSTAFA NAMIDURU

İLKAY KARAOĞLAN

AYŞE ÖZLEM METE

Invasive device-associated hospital infection rates, etiological agents, and their antibiotic susceptibilities in the medical intensive care unit of a university hospital in Turkey

Saliha ÇEVİK, Vuslat BOŞNAK*, Mustafa NAMIDURU, İlkay KARAOĞLAN, Ayşe Özlem METE
Department of Infectious Diseases and Clinical Microbiology, Faculty of Medicine, Gaziantep University, Gaziantep, Turkey

Aim: To determine the rate, etiological agents, antibiotic susceptibilities, and empirical treatment options of etiological agents of invasive device-associated hospital infections (IDAHIs) in the medical intensive care unit of a university hospital.

Materials and methods: Between February 2007 and December 2009, 780 IDAHI cases were evaluated in 1650 patients.

Results: Ventilator associated pneumonia, catheter-associated urinary tract infection, and central venous catheter-associated blood stream infection were observed in 415, 242, and 143 IDAHI cases, respectively. The most frequently isolated etiological agents were *Acinetobacter* spp. in ventilator-associated pneumonia, coagulase-negative staphylococci (CoNS) in central venous catheter-associated blood stream infection, and *Candida* spp. and *E. coli* in catheter-associated urinary tract infection.

Conclusion: In our study, oxacillin resistance in coagulase-positive *S. aureus* and CoNS was high. Glycopeptides and linezolid should be considered as treatment options. Resistance of enteric bacteria is defined high against cephalosporin, aminoglycoside, and quinolone. Carbapenems can be considered in the empirical treatment of enteric bacterial infections. Colistin can be given in the treatment of resistant *Acinetobacter* infections as a therapeutic option. Since antifungal resistance is low, fluconazole should be the first drug of choice in the treatment of candidal infections.

Key words: Intensive care unit, invasive devices, antibiotic susceptibilities, nosocomial infections, surveillance

1. Introduction

Hospital infections, which are the most important cause of morbidity and mortality in intensive care units (ICUs), increase the duration of hospitalization and treatment costs. Severity of underlying diseases, wide spectrum antibiotic use, and frequency of invasive procedures cause increased infection rates in ICUs. The majority of these infections can be prevented by routine surveillance programs and infection control measures. Evaluation of invasive device-associated hospital infections (IDAHI), mainly for calculation of ICU infection rates, is a more useful method to compare the rates both within and between hospitals. Therefore, infections can be compared in patients who are confronted with the same risk.

This study was performed in the medical intensive care unit (MICU) of our hospital to define factors in IDAHI rates and antibiotic susceptibility of causative factors.

2. Materials and methods

Adult patients who were 16 or older and hospitalized

for longer than 48 h in the 28-bed MICU at the Medical Faculty Hospital of Gaziantep University between February 2007 and December 2009 were enrolled in the study. The medical records of 1650 patients (447 patients in 2007, 618 patients in 2008, and 585 patients in 2009) were reviewed retrospectively for hospital infections related to invasive device, causative microorganisms, and their susceptibility to antibiotics.

The Medical Faculty Hospital of Gaziantep University has 934 patient beds and is located in southeast Turkey. The MICU is located on the second floor and it provides intensive care unit service for patients who are hospitalized, and it has a total capacity of 28 patient beds with 16 isolation rooms. The staff is composed of a constant academic member, research assistants, and a nurse for every 3 beds during the day and night.

Invasive device-related infection surveillance is performed with patient- and laboratory-based active surveillance methods by an infection control physician and infection control nurse. Information about patients is

recorded on the patient monitoring form during their stay in the MICU by visits every day during the week. Invasive device-related infections are diagnosed according to definition criteria given by the Centers for Disease Control and Prevention (CDC). As hospital infections are based on CDC and calculations of infection rates are based on recommendations of the National Nosocomial Infection Surveillance system (NNIS), invasive device use rates are calculated by the "invasive device use days/hospitalization days" formula, and IDAHI rates are calculated by the "device associated hospital infection number in 1-year time/invasive device use days × 1000" formula (1). Device use rates and invasive device related infection rates are compared with data from the National Healthcare Safety Network (NHSN).

Peripheral blood cultures and blood cultures from the catheters, which were taken from patients followed up at ICU-IMs with the preliminary diagnosis of invasive device-related hospital infections (IDRHIs) and transferred under sterile conditions, were monitored under BacT/Alert (Biomerieux, France) automated blood culture system, and cultures that produced positive signals underwent further processes. They were passed over eosin-methylene-blue (EMB) and sheep blood agar plaques. Then 3–4-cm tip portions of urinary and central venous catheters (CVCs) were implanted semiquantitatively into blood agar and EMB agar under sterile conditions by the Maki method. A VITEK 2 (Biomerieux, France) fully automated device for identification and antibiogram was used for bacterial identification and antibiogram. Extended spectrum beta

lactamase production (ESBL) in *E. coli* and *Klebsiella* species, and oxacillin resistance in *Staphylococcus* species were evaluated by ESBL test panels of VITEK 2.

SPSS for Windows version 11.5 was used for data evaluation. Two independent rates were compared by Z test. Statistical level of significance was accepted as $P \leq 0.05$.

3. Results
Out of 1650 patients, 780 IDAHI cases were defined. Ventilator-associated pneumonia (VAP), catheter-associated urinary tract infection (CA-UTI), and central venous catheter-associated circulation infection (CVCA-BSI) were observed in 415, 242, and 143 IDAHI cases, respectively. Number of patients internalized into the MICU, disease days, and hospital infection incidence are shown in Table 1.

In the 3-year time period, the 3 most frequently isolated etiological agents were *Acinetobacter* spp., *Pseudomonas* spp., and coagulase-positive staphylococci (CPS) in VAP; *Acinetobacter* spp., coagulase-negative staphylococci (CoNS), and *Enterococcus* spp. in CVCA-BSI; and *E. coli*, *Candida* spp., and *Enterococcus* spp. in CA-UTI. Isolated agents in VAP, CVCA-BSI, and CA-UTI are shown in Table 2.

While oxacillin resistance according to the years was 94%, 84%, and 82% for CPS and 100%, 100%, and 84% for CoNS, vancomycin resistance according to the years was 36%, 29%, and 6% for *Enterococcus* spp.

Among the *Acinetobacter* spp. isolated from VAP, amikacin resistance in 2008 and imipenem resistance

Table 1. Rates of device-associated hospital infections.

	2007	2008	2009
Patient days	6093	7275	6369
Days on ventilator	3484	3846	3483
Rate of ventilator use	0.57	0.52	0.55
VAP rate	38.1	37.7	39.7
CVC days	2093	3342	4145
Rate of CVC use	0.47	0.46	0.65
CVCA-BSI rate	15.8	8.3	11.9
Urinary catheter days	5295	6680	6029
Rate of urinary catheter use	0.86	0.91	0.95
UCA-UTI rate	13.4	12.1	14.9

VAP: Ventilator-associated pneumonia; **CVC:** Central venous catheter; **CVCA-BSI:** CVC associated blood stream infection; **UCA-UTI:** Urinary catheter-associated urinary tract infection.

Table 2. Distribution of isolated microorganisms according to infection types, n(%).

Microorganisms	VAP			CVCA-BSI			UCA-UTI		
	2007	2008	2009	2007	2008	2009	2007	2008	2009
Acinetobacter spp.	30 (26.3)	71 (52.6)	91 (63.2)	9 (19.6)	9 (25)	11 (21.2)	5 (7.2)	4 (5.5)	10 (11.4)
Pseudomonas spp.	37 (32.5)	19 (14.1)	29 (20.1)	5 (10.8)	3 (8.3)	1 (1.9)	7 (10.1)	6 (8.2)	5 (5.7)
Klebsiella spp.	5 (4.4)	10 (14.1)	4 (2.7)	3 (6.5)	2 (5.5)	4 (7.7)	2 (2.9)	9 (12.3)	6 (6.8)
E. coli	4 (3.5)	5 (3.7)	4 (2.7)	1 (2.2)	2 (5.5)	0 (0)	26 (37.7)	14 (19.2)	10 (11.4)
PC (+) staphylococci	26 (22.9)	14 (10.4)	7 (4.8)	6 (13)	14 (10.4)	4 (7.7)	0 (0)	0 (0)	1 (1.1)
PC (–) staphylococci	1 (0.8)	3 (2.2)	1 (0.7)	8 (17.4)	4 (11.1)	18 (34.6)	0 (0)	2 (2.7)	0 (0)
Candida spp.	-	-	-	5 (10.8)	3 (8.3)	9 (17.3)	18 (26.1)	25 (34.2)	43 (48.9)
Enterococcus spp.	0 (0)	0 (0)	1 (0.7)	8 (17.4)	3 (8.3)	3 (5.8)	9 (13)	11 (15.1)	13 (14.8)
Enterobacter spp.	1 (0.8)	0 (0)	1 (0.7)	0 (0)	2 (5.5)	2 (3.8)	1 (1.4)	0 (0)	0 (0)

in 2007, 2008, and 2009 were statistically significantly increased in comparisons (P < 0.05). There was a statistically significant increase in antibiotic resistance comparisons of cefoperazone–sulbactam, ceftazidime, trimethoprim–sulfamethoxazole, and cefepime between 2007 and 2009 as well as 2008 and 2009 (P < 0.05). Resistance increases in these antibiotics are shown in the Figure.

Among the *Acinetobacter* spp. isolated in CVCA-BSI, there was no statistically significant difference in antibiotic resistance comparisons of amikacin, piperacillin tazobactam, cefepime, ceftazidime, or imipenem in 2007, 2008, or 2009 (P > 0.05). Among *E. coli*, which was the most commonly isolated agent in CA-UTI, there was no statistically significant difference in antibiotic resistance comparisons of amikacin, ciprofloxacin, piperacillin–tazobactam, cefepime, ceftazidime, or imipenem in 2007, 2008, or 2009 (P > 0.05).

It was observed that *E. coli*, one of the invasive device-related hospital infection agents, secreted ESBL at 77.4% in 2007, 71.4% in 2008, and 64.3% in 2009. However, isolated *Klebsiella* spp. secreted ESBL in 40% in 2007, 71.4% in 2008, and 28.6% in 2009.

There was no statistically significant difference between isolated ESBL positive *E. coli* numbers in comparisons of 2007, 2008, and 2009 (P > 0.05). There was a statistically
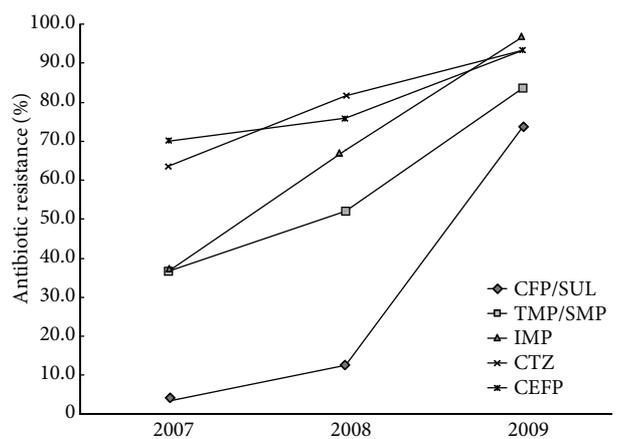
Figure. Antibiotic resistances according to years in *Acinetobacter* spp. in VAP.
CFP/SUL: Cefoperazone/Sulbactam, **TMP/SMP**: Trimethoprim/Sulfamethoxazole, **IMP**: Imipenem, **CTZ**: Ceftazidime, **CEFP**: Cefepime

significant increase in 2008 in isolated EBSL positive *Klebsiella* spp. when 2008 and 2009 were compared (P < 0.05).

Among isolated CPS *S. aureus*, oxacillin resistance was 94% in 2007, 84% in 2008, and 82% in 2009. Among CoNS,

oxacillin resistance was 100% in 2007 and 2008, whereas it was 84% in 2009. Among the *Enterococcus* spp. isolated, vancomycin resistance demonstrated a decreasing trend of 29% in 2007, 36% in 2008, and 6% in 2009. There was no statistically significant difference in oxacillin resistance in 2007, 2008, or 2009 between isolated CPS and CoNS (P > 0.05). There was no statistically significant difference in vancomycin resistance of *Enterococcus* spp. in comparisons of 2007, 2008, and 2009 (P > 0.05).

While amikacin resistance of *Acinetobacter* spp. in VAP cases was 40%–69% (P < 0.05), cefoperazone–sulbactam resistance was 3.3% in 2007 and 12.6% in 2008, but significantly increased to 73.6% in 2009 (P < 0.05). While tigecycline resistance was not evaluated in 2007, it was 5.6% and 5.5% in 2008 and 2009, respectively.

In our study, while imipenem, piperacillin–tazobactam, and cefepime resistance of *Acinetobacter* spp. isolated in 2009 from CVCA-BSI were high, it was not statistically significant when compared with that in 2007 and 2008 (P > 0.05). While there was no resistance to cefoperazone–sulbactam in 2007 and 2008, it was 54.4% in 2009. As oxacillin resistance was over 80% in all 3 years for *S. aureus*, it was 100% in 2007 and 2008 and 75% in 2009 for CoNS.

Gentamicin resistance of *E. coli* isolated from CA-UTI in our study was over 50% in all 3 years, whereas ciprofloxacin resistance was 40%–78.5% and imipenem resistance was 0%–19.2%. However, there was no statistically significant increase in antibiotic resistance of *E. coli* in 2007, 2008, or 2009 (P > 0.05).

4. Discussion

Nosocomial colonization of resistant pathogens and infection development are inevitable in ICUs, because of the many invasive procedures being performed, cross-infections due to close contact between patients and healthcare personnel, and wide-spectrum antibiotic use in these units.

When our data are compared with those of NHSN, mechanical ventilation (MV) use rates were between the 50th and 75th percentiles in 2007, 2008, and 2009, and VAP rates were over the 90th percentile. While our ventilator use rates are close to the mean values, high rates of VAP may be due to intubation under emergency conditions, incompliance with control recommendations for infections while cleaning up the mechanical ventilator circuits, elongation of ventilator support duration, underlying diseases of patients, quality of healthcare service personnel, and, most importantly, lack of hand hygiene.

CVC use rate was at the 25th percentile (low catheter use rate) in 2007 and 2008 and at the 90th percentile in 2009. However, the CVCA-BSI rate was over the 90th percentile in all 3 years. Urinary catheter use rates were over the 75th percentile in 2007 and over the 90th percentile in 2008 and 2009, whereas infection rates were over the 90th percentile, namely very high, in all 3 years. This indicated that high rates of urinary catheter use may have increased the infection rate, and so refraining from unnecessary use of urinary catheters may have decreased the UCA-UTI rate.

When our IDAHI rates are compared with those of NHSN results, the high rates showed that efforts towards infection prevention should be increased. Moreover, factors affecting the results may be long durations of patients in MICUs or nurse and healthcare personnel problems, which are encountered sometime in ICUs. The results indicate that more comprehensive studies are required to be conducted on this issue.

Dizbay et al. (2) reported from their study including ICUs of the Medical Faculty of Gazi University in Turkey that VAP rates were 38 and 34, whereas CA-UTI rates were 9 and 7.3 and CVCA-BSI rates were 15.3 and 7.4 in 2006 and 2007, respectively.

Candevir et al. (3) reported in their study including ICUs of the Medical Faculty of Çukurova University in Turkey that the VAP rate was 21, whereas CA-UTI rate was 10 and CVCA-BSI rate was 9 between 2006 and 2009. Invasive device-associated hospital infection rates in the MICUs of our university were similar to these rates.

Device-associated hospital infection rates in the ICUs of 4 hospitals in Peru in 2005 and 2006 were compared with the results of NHSN. While VAP, CVCA-BSI, and CA-ITU rates in Peru were 31.3, 7.7, and 5.1, the results of NHSN were 3.6, 2.4, and 3.4, respectively. These results were over the 90th percentile, when compared with the NHSN data. The high results in Peru indicated that efficient surveillance is required and serious studies should be performed in compliance with providing hand hygiene (4).

In a 3-year study conducted in 10 ICUs of 9 hospitals in Colombia, rates of VAP, CVCA-BSI, and CA-ITU were 10.0, 11.3, and 4.3, respectively. When these results were compared with 2004 data from NNIS, they were over the 90th percentile, and so it was concluded that more effective infection control measures are required in Colombia (5).

In a study performed in 13 ICUs of 12 hospitals in Turkey, which are members of the International Infection Control Consortium (INICC), total rates of VAP, CVCA-BSI, and CA-ITU were calculated as 26.5, 17.6, and 8.3, respectively (6). When these results were compared with NNIS data, they were over the 90th percentile, and were similar to our results.

In our study, the most frequently isolated microorganisms in VAP were *Acinetobacter* spp., which have been reported to have gained increased importance. They may cause small-scale epidemics in ICUs by infecting

immunocompromised and debilitated patients (7). In our study, the reason for frequently encountering *Acinetobacter* spp. may be similar, but additionally host factors (DM, malignancy, and previous antibiotic use history), lack of qualified personnel, and poor compliance with hand hygiene are the other reasons.

CVCs are indispensable devices applied for monitoring and treatment of patients in ICUs. It has been reported that 1 out of 20 applied CVCs caused CVCA-BSI, and more than 400,000 BSIs have been encountered annually (8). The most frequently encountered factors in CVCA-BSI were PC (–) staphylococci, *S. aureus*, aerobic gram-negative bacilli, and *Candida* spp. This order differs according to hospitals and units. In the last decade, it has been demonstrated that PC (–) staphylococci rates increased 10% in BSIs and the majority of sepsis cases associated with catheters are caused by PC (–) staphylococcus epidemics (9,10).

It has been demonstrated that CVC use increases development of candidemia 6-fold, whereas inappropriate fluconazole use increases development of candidemia 9-fold (11). In our study, CVC use was increased in 2009 when compared with the other years, and thus it is thought that one of the reasons for increased *Candida* infections might be increased use of CVCs.

The relationship between application of urinary catheters, duration of catheterization, and CA-UTI development has been demonstrated in many studies (12). In a study performed by Laupland et al. (13), the most frequently isolated agents in decreasing order were *E. coli* (23%), *Candida* spp. (20%), and *Enterococcus* spp. (15%). In our study, the high rates of *Candida* infections might have been due to long duration of urinary catheterization and wide-spectrum antibiotics used in the majority of patients.

Inappropriate antibiotic use is quite common all over the world. As a result of frequent and inappropriate antibiotic use in ICUs, infections with multiple drug resistant microorganisms develop and difficulties are experienced in treating them. Especially the use of third generation cephalosporin, fluoroquinolone, and carbapenem derivatives plays an important role in the development of infections, which are caused by resistant microorganisms (14). In general, antibiotic resistance rates in ICUs in Turkey are higher than those in ICUs at NNIS hospitals in the USA (15). According to NNIS reports, methicillin-resistant *S. aureus* isolates (89.2% vs. 48.1%), ceftriaxone-resistant *Enterobacter* spp. (48.2% vs. 48.1%), and fluoroquinolone-resistant *P. aeruginosa* (51.1% vs. 29.1%) have been defined. High resistance rates are observed against all wide-spectrum antibiotics, which have been used commonly in ICUs (16).

Resistance rates of infectious agents causing device-related hospital infections were reported as 89.2% for *S.*

aureus against methicillin, 87.1% for *Acinetobacter* spp. against piperacillin–tazobactam, 48.2% for *Enterobacter* spp. against ceftriaxone and 52% against piperacillin–tazobactam, 51.1% for *P. aeruginosa* against ciprofloxacin and 38.7% against imipenem, and 1.9% for *Enterococcus* spp. against vancomycin in a multicenter study performed in Turkey (6).

In Peru, infectious agents for device-associated hospital infections in ICUs of 4 hospitals, which were INICC members, were 73.5% methicillin-resistant *S. aureus,* 62% ceftazidime-resistant *Pseudomonas aeruginosa*, 36.1% imipenem-resistant *Pseudomonas* spp., and 40.8% ceftazidime-resistant *Enterobacter* spp. (4).

According to these results, high antibiotic resistance of microorganisms may be related to initiation of inappropriate antibiotics and unnecessary antibiotic use with long stay of patients in MV, which may cause elongated ICU durations, and so colonized microorganisms become pathogens and gain resistance to the antibiotics given.

When surveillance data for 2007–2009 were evaluated, our IDAHI rates were high. Moreover, in prevention of infections in patients, decreasing IDAHI rates like VAP, CVCA-BSI, and CA-UTI becomes a fatal and cardinal issue. Our main aim is to protect the patient from infections, and so increasing compliance, complete attendance of training programs, and strict checking of compliance should be ensured. Moreover, rational policies for antibiotic use should be constituted. Increased vancomycin consumption is known to have a significant role in observations of vancomycin-resistant enterococci and staphylococci with decreased vancomycin susceptibility.

Surveillance data for 2007–2009 have guided us as to which empirical treatments should be used in invasive device-associated nosocomial infections in ICUs. The most commonly isolated microorganism in VAP is *Acinetobacter* spp. The preferred antibiotics may be amikacin, cefoperazone–sulbactam, and colistin. Although these antibiotics can be used for empirical treatments due to their low resistance rates, because of their rapidly developed resistance profile antibiograms should be studied. Although *Acinetobacter* spp. have been observed to be susceptible to tigecycline, it should not be the first line drug because of its low penetration rate into the lung parenchyma.

The most commonly isolated agents in CVCA-BSIs are *Acinetobacter* spp., and PC (–) staphylococci are second. Because of high oxacillin resistance, glycopeptides can be preferred empirically in the presence of gram-positive bacteria. However, as infection rates with staphylococci are decreased, antibiotherapy based on culture/antibiogram is more appropriate than empirical treatment.

The most common agent for CA-UTI is *E. coli*. In empirical treatments in *E. coli* infections, resistance

to ciprofloxacin, amikacin, and cefepime should be considered.

5. Conclusions

In order to decrease high invasive device-associated hospital infection rates, continuation of surveillance should be provided, unnecessary MV and catheter use should be avoided, and patients should be detached from ventilators and catheters removed as soon as possible. Increasing compliance to standard isolation measures, qualified personnel training, and hand hygiene should be considered.

In our study, oxacillin resistance in CPS and CoNS was high. Methicillin resistance should be considered while empirical treatment for staphylococcus infection is planned in the Intensive Care Unit of Internal Medicine (ICU-

IM). Glycopeptides and linezolid should be considered as treatment options. Resistance of enteric bacteria is high against cephalosporin, aminoglycoside, and quinolone. Carbapenems can be considered in the empirical treatment of enteric bacterial infections. Resistance of *Acinetobacter* spp. to amikacin and cefoperazone is increased over time. Colistin can be given in the treatment of resistant *Acinetobacter* infections as a therapeutic option. Since antifungal resistance is low, fluconazole should be the first drug of choice in treatment of candidal infections.

Data obtained by routine surveillance are important for follow up of infection and antibiotic resistance rates. In line with these data, strategies for prevention of infections can be developed and empirical treatment protocols can be prepared.

References

1. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of healthcare-associated infection and criteria for specific types of infections in the acute care setting. Am J Infect Control 2008; 36: 309–32.

2. Dizbay M, Bas S, Gursoy A, Simşek H, Maral I, Aktas F. Invasive device-related infection surveillance in intensive care units of Gazi University Hospital in 2006–2007. Türkiye Klinikleri Journal of Medical Sciences 2009; 29: 140–5.

3. Candevir A, Kurtaran B, Kibar F, Karakoç E, Aksu HSZ, Taşova Y. Invasive device-associated nosocomial infections of a teaching hospital in Turkey; four years' experience. Turk J Med Sci 2011; 41: 137–147.

4. Cuellar LE, Fernandez-Maldonado E, Rosenthal VD, Castaneda-Sabogal A, Rosales R, Mayorga-Espichan MJ et al. Device-associated infections rates and mortality in intensive care units of Peruvian Hospitals. International Nosocomial Infection Control Consortium (INICC) findings. Pan American Journal of Public Health 2008; 24: 16–24.

5. Moreno CA, Rosenthal VD, Olarte N, Gomez WV, Sussmann O, Agudelo JG et al. Device-associated infection rate and mortality in intensive care units of 9 Colombian hospitals: findings of the International Nosocomial Infection Control Consortium. Infection Control and Hospital Epidemiology 2006; 27: 349–56.

6. Leblebicioğlu H, Rosenthal VD, Arıkan OA, Özgültekin A, Yalcin AN, Köksal I et al. Device-associated hospital-acquired infection rates in Turkish intensive care units. Findings of the International Nosocomial Infection Control Consortium (INICC). J Hosp Infect 2007; 65: 251–7.

7. Jain R, Danziger LH. Multidrug-resistant acinetobacter infections: an emerging challenge to clinicians. Ann Pharmacother 2004; 38: 1449–59.

8. Raad H, Fang X, Keutgen MX, Jiang Y, Sherertz R, Hachem R. The role of chelators in preventing biofilm formation and catheter-related bloodstream infections. Curr Opin Infect Dis 2008; 21: 385–92.

9. Mermel LA, Farr BM, Sheretz RJ, Raad II, O'Grady N, Harris JS et al. Guidelines for the management of intravascular catheter-related infections. Clin Infect Dis 2001; 32: 1249–72.

10. O'Grady NP, Alexander M, Dellinger EP, Gerberding JL, Heard SO, Maki DG et al. Guidelines for the prevention of intravascular catheter-related infections. MMWR 2002; 51/RR-10; 1–29.

11. Labelle A, Micek ST, Roubinian N, Kollef M. Treatment-related risk factors for hospital mortality in Candida bloodstream infections. Crit Care Med 2008; 36: 2967–72.

12. Graves N, Tong E, Morton A, Halton K, Curtis M, Lairson D et al. Factors associated with health care-acquired urinary tract infection. Am J Infect Control 2007; 35: 387–92.

13. Laupland K, Bagshaw S, Kirkpatrick AW, Ross T, Church DL. Intensive care unit- acquired urinary tract infections in a regional critical care system. Crit Care Med 2005; 9: 60–5.

14. Stefani S, Varaldo PE. Epidemiology of methicillin resistant staphylococci in Europe. Clin Microbiol Inf 2003; 9: 1179–86.

15. Saba R, İnan D, Turhan Ö, Yalçın AN, Günseren F, Mamıkoğlu L. Surveillance of antimicrobial use in a Turkish university hospital. Turk J Med Sci 2011; 41: 701–710.

16. Safdar N, Maki DG. The commonality of risk factors for nosocomial colonization and infection with antimicrobial-resistant *Staphylococcus aureus*, *Enterococcus*, Gram- negative bacilli, *Clostridium difficile* and *Candida*. Ann Intern Med 2002; 136: 834–4.