Journal of Infection (2014) 68, 131–140

BIA British Infection Association

www.elsevierhealth.com/journals/jinf

Surveillance, control and management of infections in intensive care units in Southern Europe, Turkey and Iran – A prospective multicenter point prevalence study

Hakan Erdem [a,*], Asuman Inan [b], Selma Altındis [c], Biljana Carevic [d], Mehrdad Askarian [e], Lucy Cottle [f], Bojana Beovic [g], Akos Csomos [h], Krassimir Metodiev [i], Sead Ahmetagic [j], Arjan Harxhi [k], Lul Raka [l], Krsto Grozdanovski [m], Mihai Nechifor [n], Emine Alp [o], Fatma Bozkurt [p], Salih Hosoglu [p], Ismail Balik [q], Gulden Yilmaz [q], Matjaz Jereb [g], Fatemeh Moradi [r], Nikolay Petrov [s], Selcuk Kaya [t], Iftihar Koksal [t], Turan Aslan [u], Nazif Elaldi [v], Yasemin Akkoyunlu [u], Seyyed Alireza Moravveji [w], Gabor Csato [x], Balazs Szedlak [y], Filiz Akata [z], Serkan Oncu [aa], Svjetlana Grgic [ab], Gorana Cosic [ac], Chavdar Stefanov [ad], Mehrdad Farrokhnia [ae], Mária Müller [af], Catalina Luca [n], Nada Koluder [ag], Volkan Korten [ah], Viliyan Platikanov [ai], Petja Ivanova [ai], Soheil Soltanipour [aj], Mahmood Vakili [ak], Saman Farahangiz [al], Abdorrahim Afkhamzadeh [am], Nicholas Beeching [f], Salman Shaheer Ahmed [o], Alma Cami [an], Ramin Shiraly [ao], Anja Jazbec [ap], Tomislav Mirkovic [aq], Hakan Leblebicioglu [ar], Kurt Naber [as]

[a] *GATA Haydarpasa Training Hospital, Department of Infectious Diseases and Clinical Microbiology, Istanbul, Turkey*
[b] *Haydarpasa Numune Training and Research Hospital, Department of Infectious Diseases and Clinical Microbiology, Istanbul, Turkey*
[c] *Sakarya University, Faculty of Management, Department of Health Administration, Sakarya, Turkey*
[d] *Clinical Center of Serbia (CCS), Department for Hospital Epidemiology, Belgrade, Serbia*
[e] *Department of Community Medicine, School of Medicine, Medicinal & Natural Products Chemistry Research Centre, Shiraz University of Medical Sciences, Shiraz, Iran*

* Corresponding author. Enfeksiyon Hastalıkları Klinigi,GATA Haydarpasa Eğitim Hastanesi, Uskudar, Istanbul, Turkey. Tel.: +90 532 7842024.
E-mail addresses: hakanerdem1969@yahoo.com (Erdem).

http://dx.doi.org/10.1016/j.jinf.2013.11.001

[f] *Royal Liverpool University Hospital, United Kingdom*
[g] *University Medical Centre, Department of Infectious Diseases, Ljubljana, Slovenia*
[h] *Semmelweis University, Department of Anaesthesia and Intensive Care, Budapest, Hungary*
[i] *Medical University, Department of Preclinical and Clinical Sciences, Varna, Bulgaria*
[j] *University Clinical Center Tuzla, Department for Infectious Diseases, Tuzla, Bosnia and Herzegovina*
[k] *University Hospital Center of Tirana, Service of Infectious Disease, Tirana, Albania*
[l] *University of Prishtina, School of Medicine & National Institute of Public Health of Kosova, Prishtina, Kosova, Serbia*
[m] *University Clinic for Infectious Diseases, Department of Intensive Care, Skopje, Macedonia*
[n] *Gr. T. Popa University of Medicine and Pharmacy, Department of Pharmacology, Iasi, Romania*
[o] *Erciyes University School of Medicine, Department of Infectious Diseases and Clinical Microbiology, Kayseri, Turkey*
[p] *Dicle University School of Medicine, Department of Infectious Diseases and Clinical Microbiology, Diyarbakir, Turkey*
[q] *Ankara University School of Medicine, Department of Infectious Diseases and Clinical Microbiology, Ankara, Turkey*
[r] *Clinical Research Center on Infectious Diseases and Tropical Medicine, Bandar Abbas, Iran*
[s] *Military Medical Academy, Department Anaesthesiology and Intensive Care, Sofia, Bulgaria*
[t] *Karadeniz Technical University School of Medicine, Department of Infectious Diseases and Clinical Microbiology, Trabzon, Turkey*
[u] *Bezmi Alem University School of Medicine, Department of Infectious Diseases and Clinical Microbiology, Istanbul, Turkey*
[v] *Cumhuriyet University School of Medicine, Department of Infectious Diseases and Clinical Microbiology, Sivas, Turkey*
[w] *Kashan University of Medical Sciences, Trauma Research Center, Department of Community Medicine, Kashan, Iran*
[x] *Kenézy Hospital, Department of Anesthesiology and Intensive Care, Debrecen, Hungary*
[y] *Borsod County Hospital and Teaching Hospital, Department of Anaesthesiology and Intensive Therapy, Miskolc, Hungary*
[z] *Trakya University, School of Medicine, Department of Infectious Diseases and Clinical Microbiology, Edirne, Turkey*
[aa] *Adnan Menderes University School of Medicine, Department of Infectious Diseases and Clinical Microbiology, Aydin, Turkey*
[ab] *University Hospital Clinic for Infectious Diseases, Mostar, Bosnia and Herzegovina*
[ac] *IPH of Vojvodina, Department of Prevention and Control of Diseases, Medical Faculty, University of Novi Sad, Serbia*
[ad] *University Multiprofile Hospital for Active Treatment, Department of Anesthesiology and Intensive Treatment, St. Georgi, Plovdiv, Bulgaria*
[ae] *Kerman University of Medical Sciences, Department of Internal Medicine, Kerman, Iran*
[af] *Markhot Hospital, Department of Anaesthesiology and Intensive Care, Eger, Hungary*
[ag] *Clinic for Infectious Diseases, Sarajevo, Bosnia and Herzegovina*
[ah] *Marmara University, School of Medicine, Department of Infectious Diseases and Clinical Microbiology, Istanbul, Turkey*
[ai] *University Hospital "St. Marina", Department of Anesthesiology and ICM, Varna, Bulgaria*
[aj] *Guilan University of Medical Sciences, School of Medicine, Department of Community Medicine, Rasht, Iran*
[ak] *Shahid Sadoughi University School of Medicine, Department of Community Medicine, Yazd, Iran*
[al] *Department of Community Medicine, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran*
[am] *Department of Community Medicine, Faculty of Medicine, Kurdistan University of Medical Sciences, Sanandaj, Iran*
[an] *University Hospital of Pulmonary Disease, Intensive Care Clinic, Tirana, Albania*
[ao] *Ilam University of Medical Sciences, Department of Community Medicine, Yazd, Iran*
[ap] *University Clinical Center Ljubljana, Center for Intensive Internal Medicine, Ljubljana, Slovenia*
[aq] *University Medical Centre Ljubljana, Department of Anestesiology and Surgical Intensive Care, Ljubljana, Slovenia*
[ar] *Ondokuz Mayis University School of Medicine, Department of Infectious Diseases and Clinical Microbiology, Samsun, Turkey*
[as] *Technical University of Munich, Munich, Germany*

Accepted 1 November 2013
Available online 20 November 2013

KEYWORDS
ICU;
Infection;
Turkey;
Europe;
Iran;
Resistance

Summary *Objective:* We aimed to compare the features of intensive care units (ICUs), their antimicrobial resistance patterns, infection control policies, and distribution of infectious diseases from central Europe to Mid-West Asia.
Methods: A cross-sectional point prevalence study was performed in 88 ICUs from 12 countries. Characteristics of ICUs, patient and antibiotic therapy data were collected with a standard form by infectious diseases specialists.
Results: Out of 749, 305 patients at least with one infectious disease were assessed and 254 patients were reported to have coexistent medical problems. When primary infectious diseases diagnoses of the patients were evaluated, 69 had community-acquired, 61 had healthcare-associated, and 176 had hospital-acquired infections. Pneumonia was the most frequent ICU infection seen in half of the patients. Distribution of frequent pathogens was as follows: Enteric Gram-negatives ($n = 62$, 28.8%), Acinetobacter *spp.* ($n = 47$, 21.9%), *Pseudomonas aeruginosa* ($n = 29$, 13.5%). Multidrug resistance profiles of the infecting microorganisms seem to have a uniform pattern throughout Southern Europe and Turkey. On the other hand, active and device-associated infection surveillance was performed in Turkey more than Iran and Southeastern Europe ($p < 0.05$). However, designing antibiotic treatment according to culture results was highest in Southeastern Europe ($p < 0.05$). The most frequently used antibiotics were carbapenems ($n = 92$, 30.2%), followed by anti-gram positive agents (vancomycin, teicoplanin, linezolid, daptomycin, and tigecycline; $n = 79$, 25.9%), beta-lactam/beta lactamase inhibitors ($n = 78$, 25.6%), and extended-spectrum cephalosporins ($n = 73$, 23.9%).
Conclusion: ICU features appears to have similar characteristics from the infectious diseases perspective, although variability seems to exist in this large geographical area.

Introduction

The management of infections within the intensive care unit (ICU) poses challenges due to the severity of illness, complex comorbidities, multiple invasive procedures and impaired host defenses characteristic of this patient population. The frequency, epidemiology, microbial spectrum, and antimicrobial resistance patterns vary between countries and even between institutions.[1–3] Surveillance of infections and antimicrobial stewardship within the ICU setting are essential pillars of effective health care, not only for the prevention of infection but also for rapid and effective management and conservation of an increasingly limited range of treatment options.[4] However, there are limited data from developing countries.[5] Infections with multidrug resistant organisms such as *Acinetobacter spp.* are known to be specific problems in this region but large-scale surveys have not been performed to compare countries simultaneously.[2,3,6]

The primary objective of this study was to compare ICUs with respect to infection prevention and control measures, causative microorganisms, antibiotic resistance patterns, and antibiotic usage, in a large geographical area ranging from Central Europe to Mid-western Asia. In addition, the study aimed to describe the range of infection syndromes within these ICUs as well as illness severity and patient comorbidities, both of which directly affect outcome in ICU patients with infection.

Material and methods

This cross-sectional point prevalence study was carried out on a single day between June 15 and July 01 of 2012. ICUs from Slovenia, Hungary, Bosnia-Herzegovina, Kosovo, Serbia, Romania, Macedonia, Albania, Bulgaria, Turkey, and Iran collaborated in this study. The cities in which the participating centers were located are shown in Fig. 1. The only military institution joined in this study was a Bulgarian center. No other data from military institutions were included. On the study day, each patient in the participating ICU was visited by an infectious disease specialist. Data collection for patients with infection involved consultation of the patient files, nursing records, infection control committee records, and the hospital computer system. General characteristics of ICUs were also obtained for comparison.

Community-acquired, healthcare-associated, and hospital-acquired infections were defined using the criteria of the Centers for Diseases Control and Prevention (CDC). Sepsis definitions were made according to the sepsis consensus.[7] Multidrug resistance (MDR) was defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories. Extensive drug-resistance (XDR) was defined as non-susceptibility to at least one agent in all but two or fewer antimicrobial categories (i.e. bacterial isolates remain susceptible to only one or two categories). Pan drug-resistance (PDR) was defined as non-susceptibility to all agents in all antimicrobial categories.[8] Vancomycin, teicoplanin, linezolid, daptomycin, and tigecycline were defined as the anti-Gram positive agents while levofloxacin, moxifloxacin, and gemifloxacin were grouped as respiratory quinolones. beta lactam-beta/lactamase inhibitor combinations used in the study included ampicillin/sulbactam, amoxicillin/clavulanic acid, piperacillin–tazobactam, and cephaperazone–sulbactam. Cefuroxime, ceftriaxone, cefotaxime, ceftazidime, and cefepime were classified as extended-spectrum cephalosporins.

Statistical analyses were performed with SPSS 17.0 (SPSS Inc., Chicago, IL, USA). Results were given as mean ± standard deviation, and frequencies, and percentages for categorical variables. Comparisons in more than two groups were performed with one-way ANOVA followed

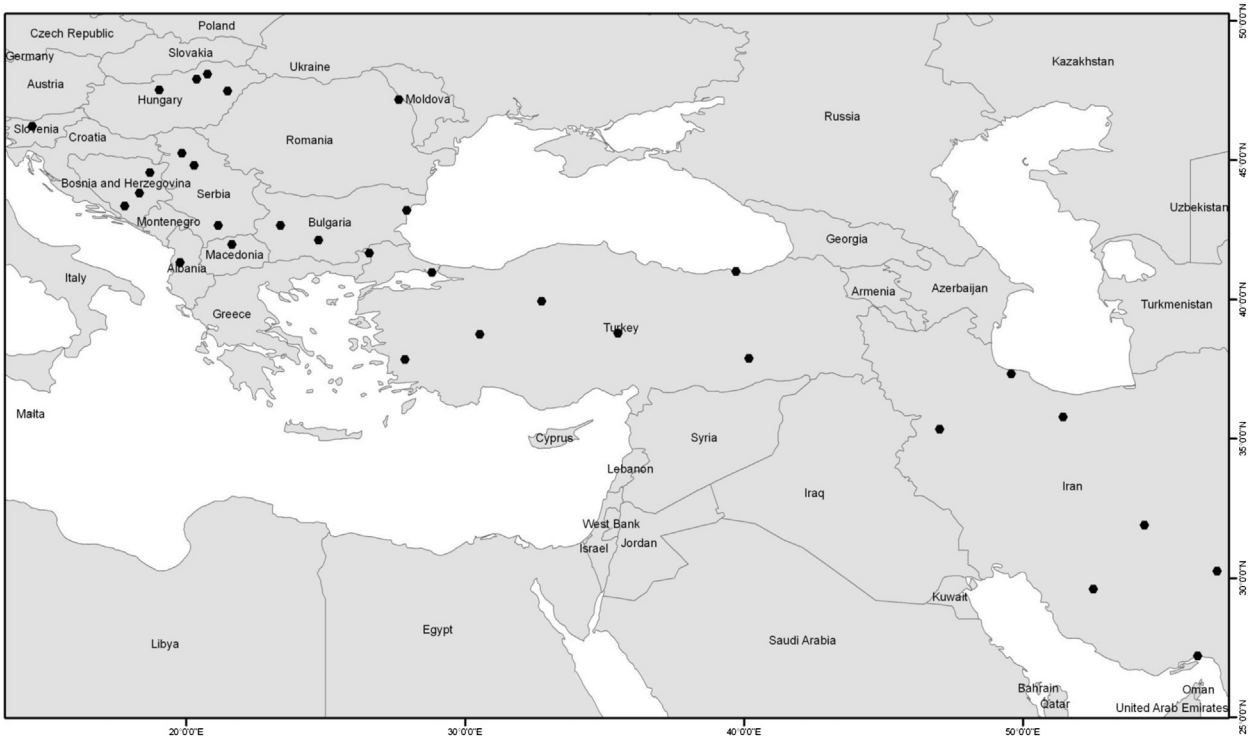

Figure 1 The cities in which the participating centers were located.

by a post hoc Tukey test or Kruskal–Wallis variance analysis, as appropriate. Chi-square test or the Freeman–Halton extension of the Fisher exact probability test for a two-rows by three-columns contingency table were used for the comparisons of categorical variables.[9] All comparisons were two-tailed and a p-value of <0.05 was accepted as statistically significant.

Results

In this study 749 patients were receiving care in 88 participating ICUs in 11 countries on the study day. Of these, 305 (40.7%) had at least one infection and were included in the analysis.

ICU characteristics

The distribution of participating ICUs were as follows: 15 general surgery ICUs ($n = 34$), 7 neurosurgical ICUs ($n = 31$), 8 cardiovascular surgical ICUs ($n = 9$), 11 internal medicine ICUs ($n = 34$), 7 infectious diseases ICUs ($n = 34$), 5 respiratory ICUs ($n = 27$), 5 coronary ICUs ($n = 12$), 3 neurological ICUs ($n = 8$), and 27 mixed ICUs ($n = 116$). Overall 58 out of 88 ICUs (66.7%) had isolation rooms. Bed capacity and other features of participating units are shown in Tables 1and 2.

Patient demographics

Three hundred and five patients with infectious diseases were assessed (196 males). The mean (SD) age of the patients was 56.5 ($\pm$19.5) years and 254 (83.3%) were reported to have coexistent medical problems. The distribution of concomitant disease, illness severity parameters, and the devices used are presented in Table 3. 85 (27.8%) patients underwent surgery prior to their admission to ICU, while 91 (29.8%) patients underwent surgical intervention during their stay in ICU. The range of surgical procedures performed on patients during their ICU admission was as follows: 32 abdominal, 22 cardiothoracic, 26 intracranial, 8 orthopedic and 3 urogenital. 150 (49%) of ICU patients with infections underwent surgery following step down from ICU beds.

Infection syndromes

When the primary infectious diseases diagnoses of the 305 patients were evaluated, 69 (22.6%) patients had community-acquired, 61 (20%) had healthcare-associated, and 176 (57.7%) had hospital-acquired infections. The range of community-acquired infections was as follows: pneumonia ($n = 40$, 13.1%), skin and soft tissue infection ($n = 10$, 3.3%), gastrointestinal infection ($n = 7$, 2.3%), bloodstream infection ($n = 5$, 1.6%), urinary tract infection ($n = 4$, 1.3%), botulism ($n = 1$), Hantavirus hemorrhagic fever with renal syndrome ($n = 1$), empyema ($n = 1$), infective endocarditis ($n = 1$). Two patients admitted to hospital with community-acquired infections developed superimposed nosocomial infection. On the other hand, the range of healthcare-associated infections was as follows: Pneumonia ($n = 21$, 6.9%), bloodstream infection ($n = 15$, 4.9%), urinary tract infection ($n = 7$, 2.3%), surgical site infection ($n = 7$, 2.3%), skin and soft tissue infection ($n = 6$, 1.9%), gastrointestinal tract infections ($n = 2$, 0.7%), infective endocarditis ($n = 2$, 0.7%), and fulminant hepatitis B ($n = 1$, 0.3%). The distribution of infectious

Table 1 The bed capacities of the participant hospitals and the ICUs according to country groups and ICU types.

	No. of participants	Bed capacity		
		Mean (SD)	Min.	Max.
Southeast Europe				
Hospitals	17	1137 (657)	129	2145
ICUs	28	12.6 (5.53)	4	26
Medical	9	8.0 (3.12)	4	10
Surgical	7	13.1 (6.01)	5	20
Mixed type	12	15.8 (4.45)	10	26
Turkey				
Hospitals	8	946 (498)	455	1935
ICUs	44	10.82 (4.29)	4	21
Medical	17	11.65 (4.28)	7	21
Surgical	16	10.81 (5.14)	4	20
Mixed type	11	9.54 (2.66)	6	12
Iran				
Hospitals	8	457 (391)	16	1300
ICUs	16	7.75 (3.61)	1	16
Medical	5	9.00 (4.53)	5	16
Surgical	7	7.14 (3.72)	5	12
Mixed type	4	7.25 (2.50)	4	10
Overall				
Hospitals	33	925.94 (618.2)	16	2145
ICUs	88	10.83 (4.85)	1	26
Medical	31	10.16 (4.24)	4	21
Surgical	30	11.96 (4.93)	1	20
Mixed type	27	10.50 (5.33)	4	26

ICU: Intensive care unit; SD: Standard deviation.

diseases across different ICU types is summarized in Table 4 and according to their sources in Fig. 2.

Culture yield/microbiological diagnosis

In total, 358 clinical infections were identified in 305 patients. Microbiological diagnoses were established by culture in 160 patients. The mean hospitalization period before a positive culture was 18.3 ± 24.8 days while the mean ICU hospitalization before a positive culture was 16.2 ± 24.2 days. The duration of antibiotic use before positive cultures was 10 ± 15.1 days. The infecting microorganisms were as follows: enteric Gram-negative bacteria (n = 62, 28.8%) [*Escherichia coli* (n = 23), *Klebsiella spp.* (n = 23), *Enterobacter spp.* (n = 6), *Serratia marcescens* (n = 4), *Proteus spp.* (n = 6)], Acinetobacter *spp.* (n = 47, 21.9%), *Pseudomonas aeruginosa* (n = 29, 13.5%), *Stenotrophomonas maltophilia* (n = 2), *Neisseria meningitidis* (n = 1), *Neisseria spp.* (n = 1), *Sphingomonas paucimobilis* (n = 1), *Staphylococcus aureus* (n = 17, 8%), coagulase-negative Staphylococci (n = 9, 4.2%), Enterococci (n = 17, 8%), *Streptococcus viridans* (n = 7), *Streptococcus pneumoniae* (n = 6), *Clostridium difficile* (n = 3), *Candida albicans* (n = 3), *Candida non-albicans* (n = 9, untyped), *Aspergillus fumigatus* (n = 1).

Antimicrobial therapy

Before ICU admission, 135 patients (44%) had a previous hospitalization in any institution and 58 (19%) had been

Table 2 Comparison of intensive care unit (ICU) characteristics according to country groups and ICU types. Bold values represent statistically significance.

Variable	Overall	Southeast Europe	Turkey	Iran	p Value
Nurse per bed, (mean ± SD)					
Medical ICU	1.61 ± 1.33	2.10 ± 0.99	0.99 ± 0.44[a]	2.83 ± 2.55	**0.007**
Mixed type ICU	1.88 ± 0.88	2.29 ± 1.04	1.32 ± 0.42[b]	2.18 ± 0.30	**0.015**
Surgical ICU	1.97 ± 1.67	2.21 ± 1.34	1.22 ± 0.88[c]	3.42 ± 2.39	**0.008**
Nurse per patient, (mean ± SD)					
Medical ICU	0.66 ± 0.85	1.17 ± 1.47	0.39 ± 0.11	0.66 ± 0.34	0.077
Mixed type ICU	0.57 ± 0.23	0.56 ± 0.24	0.49 ± 0.12[d]	0.84 ± 0.24	**0.021**
Surgical ICU	0.77 ± 0.85	0.52 ± 0.25	0.57 ± 0.31[e]	1.47 ± 1.57	**0.039**
Written hospital antibiotic policy, *n/N* (%)	19/88 (21.6)	7/28 (25)	6/44 (13.6)	6/16 (38)	0.12
Active infection surveillance, *n/N* (%)	68/88 (77.3)	20/28 (71.4)	44/44 (100)	4/16 (25)	**<0.00001**
Device-associated surveillance, *n/N* (%)	59/88 (67)	11/28 (39.3)	43/44 (97.7)	5/16 (31.3)	**<0.00001**
Incidence density calculation, *n/N* (%)	63/88 (71.6)	15/28 (53.6)	42/44 (95.4)	6/16 (38)	**<0.00001**
Antibiotic usage rate in the study day (mean ± SD)					
Medical ICU	0.47 ± 0.28	0.57 ± 0.31	0.46 ± 0.28	0.34 ± 0.22	0.32
Mixed type ICU	0.46 ± 0.24	0.50 ± 0.21	0.46 ± 0.29	0.38 ± 0.18	0.68
Surgical ICU	0.59 ± 0.71	0.37 ± 0.22	0.45 ± 0.27	1.14 ± 1.32	0.06
Culture-based treatment *n/N* (%)					
Medical ICU	48/115 (41.7)	15/34 (44.1)	29/71 (40.8)	4/10 (40)	0.95
Mixed type ICU	72/116 (62.1)	48/69 (69.6)	23/42 (54.8)	1/5 (20)	**0.04**
Surgical ICU	40/74 (54.1)	22/24 (91.7)	15/33 (45.4)	3/17 (17.6)	**<0.00001**
Overall	160/305 (52.5)	85/127(66.9)	67/146 (45.9)	8/32 (25)	**<0.00001**

[a] Significant difference from Iran (p = 0.011). Tukey test.
[b] Significant difference from Southeast Europe (p = 0.015). Tukey test.
[c] Significant difference from Iran (p = 0.007). Tukey test.
[d] Significant difference from Iran (p = 0.016). Tukey test.
[e] Significant difference from Iran (p = 0.045). Tukey test.

Table 3 Characteristics of 305 patients with infection in intensive care unit (ICU).

Variable	
Age (*y*), mean ± SD	56.6 ± 19.5
Female gender, *n* (%)	109 (35.7)
Severity of illness on the study day	
Absence of clinical sepsis, *n* (%)	197 (64.6)
Sepsis, *n* (%)	73 (23.9)
Severe sepsis, *n* (%)	15 (4.9)
Septic shock, *n* (%)	20 (6.6)
Glasgow coma scale, mean ± SD (*n* = 25)[a]	8.3 ± 3.9
Apache II, mean ± SD (*n* = 235)	16.18 ± 9.9
Concomitant diseases, *n* (%)	
Cardiovascular events	134 (43.9)
Diabetes mellitus	68 (22.3)
Chronic obstructive lung disease (COPD)	49 (16.1)
Hematological malignancy	48 (15.7)
Acute renal failure	39 (12.8)
Solid organ tumor	36 (11.8)
Chronic renal disease	31 (10.1)
Peptic ulcer	17 (5.6)
Immunosuppression	12 (3.9)
Chronic liver disease	11 (3.6)
Bronchiectasis	10 (3.3)
Asplenia	4 (1.3)
Burn	3 (1.0)
None	51 (16.7)
Devices, used, *n* (%)	
Vascular catheters	
Internal jugular	95 (31.1)
Subclavian	89 (29.2)
Femoral	24 (7.9)
Hickman	2 (0.7)
Arterial	6 (2.0)
Urinary catheter	259 (84.9)
Nasogastric tube	162 (55.4)
Tracheostomy tube	64 (20.9)
Invasive mechanical ventilation	177 (58.0)
Non-invasive mechanical ventilation	32 (10.5)

[a] Patients with altered mental status.

admitted to an ICU in the preceding six months. In 101/305 (33.1%) patients, there was a history of prior antibiotic use in the wards. In 130/160 (77%) patients with subsequent positive culture results, at least one antibiotic had been given empirically after ICU admission but prior to microbiological confirmation. Antibiotics given prior to culture results becoming available included extended-spectrum cephalosporins (*n* = 54, 22.5%), carbapenems (*n* = 44, 18.3%), beta lactam-beta lactamase inhibitor combinations (*n* = 38, 15.8%), anti-Gram positive agents (*n* = 33, 13.7%), metronidazole/ornidazole (*n* = 25, 10.4%), aminoglycosides (*n* = 22, 9.1%) ciprofloxacin (*n* = 17, 7.0%), colistin (*n* = 5, 2.1%), and respiratory quinolones (*n* = 2, 0.8%). The resistance profiles of isolated microorganisms are detailed in Table 5, categorized according to country groups.

One patient with Hantavirus infection did not receive any antimicrobial agents. The number of antibiotics used is shown in Fig. 3. The most frequently used antimicrobials were carbapenems (*n* = 92, 30.2%), followed by anti-Gram positive agents (*n* = 79, 25.9%), beta lactam-beta lactamase inhibitors (*n* = 78, 25.6%), extended-spectrum cephalosporins (*n* = 73, 23.9%), ciprofloxacin (*n* = 35, 11.5%), aminoglycosides (*n* = 31, 10.2%), colistin (*n* = 31, 10.2%), metronidazole/ornidazole (*n* = 25, 8.2%), antifungals (*n* = 24, 7.9%), and respiratory quinolones (*n* = 18, 5.9%) (Fig. 4). Specific antibiotics administered to patients with infection on the study day were as follows: flucloxacillin (*n* = 3), crystallized penicillin (*n* = 5), ampicillin–sulbactam (*n* = 11), amoxicillin clavulanate (*n* = 4), piperacillin–tazobactam (*n* = 45), cefazolin (*n* = 2), cefuroxime (*n* = 2), ceftriaxone/cefotaxime (*n* = 49), ceftazidime (*n* = 18), cefepime (*n* = 5), cephaperazone–sulbactam (*n* = 17), sulbactam (*n* = 5), imipenem (*n* = 32), meropenem (*n* = 54), ertapenem (*n* = 5), amikacin (*n* = 19), gentamicin (*n* = 7), netilmicin (*n* = 1), streptomycin (*n* = 1), tobramycin (*n* = 4), aztreonam (*n* = 1), ciprofloxacin (*n* = 38), levofloxacin (*n* = 11), moxifloxacin (*n* = 7), colistin (*n* = 34), tigecycline (*n* = 8), teicoplanin (*n* = 20), vancomycin (*n* = 37), linezolid (*n* = 7), daptomycin (*n* = 7), trimethoprim/sulfamethoxazole [SXT (*n* = 6)], rifampicin (*n* = 6), clindamycin (*n* = 10), aciclovir (*n* = 6), fluconazole (*n* = 10), caspofungin (*n* = 4), voriconazole (*n* = 2), amphotericin B (*n* = 4), anidulafungin (*n* = 3), metronidazole/ornidazole (*n* = 26), clarithromycin/azithromycin (*n* = 8), lamivudine (*n* = 1), gancyclovir (*n* = 1), isoniazid (*n* = 1), pyrazinamide (*n* = 1), ethambutol (*n* = 1). Details of antibiotic administration according to ICU type and country are presented in Table 6 and Fig. 5.

Discussion

Measures to prevent and control infectious diseases in the ICUs studied in this large geographical area, extending from Central Europe to Mid-western Asia, appear to be better implemented than in many other developing countries.[10] However there were there major differences in the region for the quality indicators. First, active surveillance of infections, device-associated surveillance, and incidence density calculation for infections were enforced in more Turkish units than in Southeast Europe and Iran. The probable reason for this is that the Turkish Ministry of Health issued a ''Budget Enforcement Document'' that outlined the antibiotic prescription policy in 2003.[11] Since then Turkey has made significant advances in infection prevention including legislation pertaining to infection control, training, surveillance issues, and nationwide data analysis. Nevertheless, our data showed awareness of infection control issues in Southeast Europe and Iran. Staffing ratios are known to be important in reducing infection,[12] and nurse per bed and patient ratios were generally highest in ICUs in Iran, where official standards advocate a minimum nurse per patient ratio of one (*Prof. Dr. Mehrdad Askarian, personal communication*). Southeastern European units tailored antibiotic therapy according to culture results more frequently: antimicrobials were guided by culture

Table 4 Distribution of major groups of infectious diseases according to ICU types.[a] Bold values represent statistically significance.

Infection type	Overall (n = 305)	Medical ICUs (n = 115)	Surgical ICUs (n = 74)	Mixed ICUs (n = 116)	p Value
VAP	77 (25.2)	20 (17.4)	19 (25.7)	38 (32.8)	**0.027**
Pneumonia (other)	86 (28.2)	45 (39.1)	17 (23)	24 (20.7)	**0.004**
Catheter-related BSI	16 (5.2)	2 (1.7)	6 (8.1)	8 (6.9)	0.095
Non-catheter-related BSI	40 (13.1)	13 (11.3)	6 (8.1)	21 (18.1)	0.106
Catheter-related UTI	24 (22.8)	5 (4.3)	8 (10.8)	11 (9.5)	0.195
Non-catheter-related UTI	18 (5.9)	8 (7.0)	1 (1.4)	9 (7.8)	0.156
Surgical site infection	36 (11.8)	11 (9.6)	14 (18.9)	11 (9.5)	0.93
Skin/soft tissue infection	29 (9.5)	12 (10.4)	8 (10.8)	9 (7.8)	0.714
GIT infection	19 (6.2)	6 (5.2)	6 (8.1)	7 (6.0)	0.72
Other	13 (4.3)				

VAP: Ventilator-associated pneumonia, GIT: Gastrointestinal tract, BSI: Bloodstream infection, UTI: Urinary tract infection.
Other: Two meningoencephalitis, 3 pulmonary tuberculosis, 2 infective endocarditis, 2 empiyemas, 1 upper respiratory tract infection, 1 hantavirus pulmonary syndrome, 1 fulminant viral hepatitis B, 1 botulism.
[a] Data expressed as n (%).

results in approximately two-thirds of their patients, compared with half of infected patients in Turkish ICUs and a quarter of infected patients in Iranian ICUs.

In the EPIC I study, which was published in 1995[13] and in the EPIC II study published in 2009,[14] approximately half of patients in 1417 and 1265 ICUs respectively, were considered to have infection. Accordingly, 40.7% of ICU patients in our study had infection. The ICU mortality rate of infected patients was reported to be more than twice of noninfected patients.[14] The majority (83%) of patients included in our study had significant comorbidities, a factor which is known to influence long-term outcomes.[15,16] Cardiovascular problems were present in approximately half, followed by diabetes, chronic obstructive pulmonary disease, hematological malignancies, acute renal failure, solid organ tumors, and chronic renal disease in descending order. In addition, indwelling devices and endotracheal tubes are known to serve as portals of entry for pathogens.[17] Thus, these devices were commonly reported, including urinary catheters in the majority of patients, central venous catheters and nasogastric tubes in half, and tracheostomy tubes in one-fifth of patients. More than two-thirds of the cases were receiving ventilatory support: invasive ventilation in more than half and non-invasive ventilation in one third.

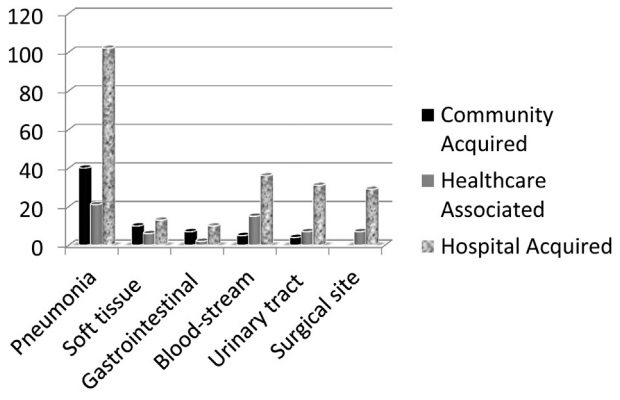

Figure 2 The distribution of common infections according to their sources.

Infection is a significant predictor of mortality in ICU patients.[14] However, only a quarter of patients in this study met the criteria for sepsis, while 5% and 7% fulfilled the criteria for severe sepsis and septic shock respectively. In both EPIC 1 and 2 studies pneumonia was the most frequent infection.[13,14] Accordingly in this study pneumonia was the leading infectious disease seen in more than half of the patients, followed by catheter-related urinary tract infection, non-catheter-related bloodstream infection, and surgical site infection, in descending order. Similarly, in another multicentre study performed in eight developing countries, ventilator-acquired pneumonia was the leading infection in 24% of cases, followed by central venous catheter-related bloodstream infection and catheter-associated urinary tract infection.[18] In addition, community-acquired and healthcare-associated infections each accounted for one-fifth of the cases while hospital-acquired infection comprised three-fifths of the cases. Pneumonia was the most common infection for both community-acquired and healthcare-associated infections. Although skin and soft tissue infection came second in the former, bloodstream infection followed pneumonia in the latter. Thus, a considerable portion of infections affecting ICU patients was acquired outside of the hospitals.

We did not detect significant differences in the distribution of infections across medical, surgical and mixed ICUs, although ventilator-unrelated pneumonias were more frequent in medical ICUs and VAPs were more frequent in mixed ICUs, as one might expect. Our results suggest that better control of VAP should be a key area for these ICUs to address, especially as recent experience in other settings has shown that VAP rates can be dramatically reduced, with better patient outcomes and substantial cost savings.[19,20] Catheter-related urinary tract infections should also be targeted, particularly as these are caused by multidrug resistant Gram-negative pathogens.

Infections due to resistant pathogens are difficult to treat and are associated with higher mortality and costs.[18,21,22] In EPIC-2 study the most common isolates

Table 5 The distribution of resistance patterns of isolated microorganisms from clinical specimens, according to country groups.[a]

Microorganism	Overall	Southeast Europe	Turkey	*p* Value[b]	Iran
Enteric Gram-negative bacilli (n = 62)					
Multidrug resistant	39 (63%)	20/34 (58.8)	18/26 (69.2)	0.43	1/2 (50)
Extensively drug resistant	5 (8%)	4/34 (11.8)	1/26 (3.8)	0.38	0
Pandrug resistant	0	0	0	ND	0
***Acinetobacter spp.* (*n* = 47)**					
Multidrug resistant	31 (66%)	19/25 (80)	11/19 (57.9)	0.33	0
Extensively drug resistant	13 (28%)	4/25 (20)	8/19 (42.1)	0.09	0
Pandrug resistant	5 (11%)	2/25 (4)	0	ND	3/3 (100)
***Pseudomonas aeruginosa* (*n* = 29)**					
Multidrug resistant	16 (55%)	7/13 (53.8)	7/14 (50)	1.0	1/2 (50)
Extensively drug resistant	7 (14%)	4/13 (30.8)	3/14 (21.4)	0.82	0
Pandrug resistant	2 (7%)	2/13 (15.4)	0	ND	0
***Staphylococcus aureus* (*n* = 17)**					
Multidrug resistant	8 (47%)	7/16 (43.8)	0	ND	1/1 (100)
Extensively drug resistant	0	0	0	ND	0
Pandrug resistant	0	0	0	ND	0
***Enterococcus spp.* (*n* = 17)**					
Multidrug resistant	10 (59%)	6/9 (66.7)	3/7 (42.9)	1.0	1/1 (100)
Extensively drug resistant	1 (6%)	0	1/7 (14.3)	ND	0
Pandrug resistant	0	0	0	ND	0

[a] Data expressed as *n*/*N* (%), ND: Not determined.
[b] Comparisons were performed between Southeast Europe and Turkey.

were *S. aureus* and *P. aeruginosa*, and each of them comprised one-fifth of culture positive cases.[14] However, enteric Gram-negative bacteria were the most frequently isolated pathogens, followed by Acinetobacter, then *P. aeruginosa*, *S. aureus* and Enterococci in descending order according to our data. This reflects the changing epidemiology in this part of the world. Multidrug resistance was seen in more than half of these microorganisms in our study. Extensive drug resistance was recorded in a considerable proportion of these isolates other than *S. aureus* and was most significant for Acinetobacter species. Finally, pandrug resistance was observed in one-tenth of Acinetobacter and *P. aeruginosa* isolates. Thus, antibiotic resistance is a major concern for ICUs in this geographical area stretching from Central Europe to Mid-western Asia.

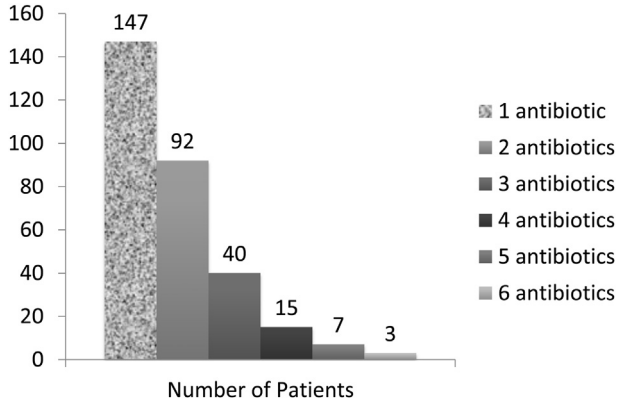

Figure 3 The number of antibiotics used in ICU patients.

High rates of ESBL-producing enteric Gram-negative bacteria, carbapenem-resistant Acinetobacter and *P. aeruginosa* strains in Turkish hospitals have long been the major focus of concern.[1,23] In a multicentre study, which evaluated 88 ICUs in 36 Turkish tertiary hospitals, rates of nosocomial infection due to *S. aureus* declined between 2008 and 2011, while hospital-acquired Acinetobacter infections increased over the same period.[6] Thus, beta lactam-beta/beta lactamase inhibitor combinations, carbapenems, and colistin were used significantly more frequently in Turkey according to our data. However, we did not find any significant difference in the antimicrobial resistance patterns between Turkey and Southeastern Europe. Of note the few PDR strains identified were only seen in Iran. Although the data is rather limited for Iran, aminoglycosides, ciprofloxacin, anti-Gram positive agents were commonly used in this country. In a recent Iranian study, 25 000 blood cultures were evaluated over five years. Half of the isolates

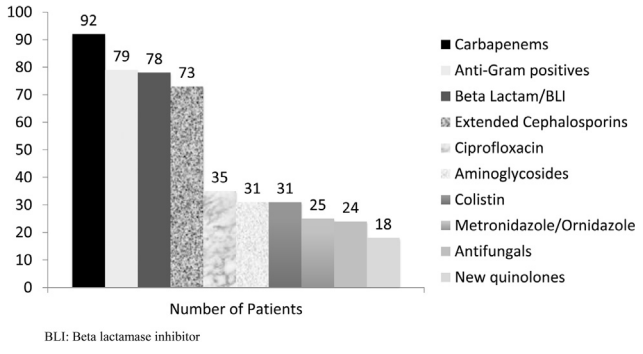

Figure 4 The number of antibiotics used in ICU patients.

Table 6 Utilization of major antibiotic groups in the treatment of infections according to the ICU type.[a] Bold values represent statistically significance.

Antibiotics in 305 patients	Surgical ICUs				Medical ICUs				Mixed ICUs			
	Southeast Europe ($n = 34$)	Turkey ($n = 71$)	*p* Value[b]	Iran ($n = 17$)	Southeast Europe ($n = 24$)	Turkey ($n = 33$)	*p* Value[b]	Iran ($n = 10$)	Southeast Europe ($n = 69$)	Turkey ($n = 42$)	*p* Value[b]	Iran ($n = 5$)
β-lactam/β-lactamase inhibitors	4 (11.8)	13 (18.3)	0.57	2 (11.8)	4 (16.7)	22 (66.7)	**0.0002**	0	12 (17.4)	20 (47.6)	**0.001**	1 (20)
Extended-spectrum cephalosporins	7 (20.6)	3 (4.2)	**0.012**	12 (70.6)	10 (41.7)	13 (39.4)	1.0	6 (60)	17 (24.6)	3 (7.1)	**0.023**	2 (40)
Carbapenems	8 (23.6)	11 (15.5)	0.42	4 (23.5)	8 (33.3)	26 (78.8)	**0.0009**	3 (30)	18 (26.1)	11 (26.2)	1.0	3 (60)
Aminoglycosides	3 (8.8)	0	**0.032**	6 (35.3)	3 (12.5)	2 (6.1)	0.64	0	16 (23.2)	0	**0.0004**	1 (20)
Ciprofloxacin	5 (14.7)	1 (1.4)	**0.013**	7 (41.1)	2 (8.3)	5 (15.2)	0.69	3 (30)	6 (8.7)	4 (9.5)	1.0	2 (40)
Respiratory quinolones	0	0	ND	0	2 (8.3)	9 (27.3)	0.09	0	7 (10.1)	0	**0.044**	0
Colistin	0	3 (4.2)	0.55	0	1 (4.1)	10 (30.3)	**0.017**	1 (10)	5 (7.2)	10 (23.8)	**0.021**	1 (20)
Anti-Gram positive antibiotics	6 (17.6)	10 (14.1)	0.77	8 (47)	9 (37.5)	16 (48.5)	0.43	6 (60)	13 (18.8)	9 (21.4)	0.81	2 (40)
Antifungals	2 (5.9)	4 (5.6)	1.0	1 (5.9)	3 (12.5)	6 (18.2)	0.72	0	3 (4.3)	3 (7.1)	0.67	2 (40)
Metronidazole	5 (14.7)	1 (1.4)	**0.013**	1 (5.9)	4 (16.7)	3 (9.1)	0.44	1 (10)	8 (11.6)	2 (4.8)	0.31	0

[a] Data presented as *n* (%). ND: Not determined.
[b] Comparisons were performed between Southeast Europe and Turkey.

Figure 5 The most frequently used antibiotics with respect to ICU type and geographical locale.

were Gram-positive bacteria, and methicillin resistance was observed in 79% and 89% of *S. aureus* and coagulase-negative staphylococci respectively. *P. aeruginosa* was the most frequent Gram-negative isolate in the same study.[24] These findings may explain the frequent use of anti-Gram positive agents, aminoglycosides, and ciprofloxacin in Iranian ICUs. In southeast Europe, aminoglycosides, extended-spectrum cephalosporins and quinolones were more frequently used compared to Turkey. Thus, differences in resistance profiles of non-lactose-fermenting bacteria isolated from this large geographical area appear to influence antimicrobial prescribing practice within individual countries included in this study.

The proportion of ICU patients receiving antibiotics did not differ significantly between countries in this study. Our findings indicate that a significant proportion of patients received treatment with "last resort" antibiotics such as colistin and carbapenems. Such empirical therapy should be minimized and should be modified according to culture results at the earliest opportunity to avoid exposing patients to the adverse effects associated with broad-spectrum agents and to limit the evolution of resistant organisms. Apparently, the establishment of a microbiological diagnosis should be improved in the region.

In conclusion, we have confirmed a worryingly high prevalence of multidrug resistant bacteria isolated from patients receiving care in a wide variety of ICUs stretching from Central Europe to Mid-western Asia. Differences in local resistance-patterns influence antibiotic prescribing practice and account for some of the inconsistencies seen between countries. The importance of establishing a microbiological diagnosis cannot be overstated, both to ensure that highly resistant pathogens are accurately identified and appropriately treated in this vulnerable ICU population, and to shorten the duration of empirical broad-spectrum antibiotic regimens that contribute to the evolution of antimicrobial resistance. Legislation is important for establishing infection control standards and seems to have contributed greatly to improve infection control in our participant countries. However, many developing countries lack legal policies requiring the establishment of infection prevention and control. Thus, this study provides a benchmark against which hospitals in this region can compare

their own performance. It provides baseline data for future studies on the success of maximizing quality interventions to contain the spread of multidrug resistant organisms and to target antimicrobial therapy more appropriately in this part of the world.

Transparency declarations

We have no competing interests to declare.
No funding of any kind was received.

References

1. Erdem H, Akova M. Leading infectious diseases problems in Turkey. *Clin Microbiol Infect* 2012;**18**(11):1056—67.
2. Shibl A, Senok A, Memish Z. Infectious diseases in the Arabian Peninsula and Egypt. *Clin Microbiol Infect* 2012;**18**(11): 1068—80.
3. Askarian M, Mansour Ghanaie R, Karimi A, Habibzadeh F. Infectious diseases in Iran: a bird's eye view. *Clin Microbiol Infect* 2012;**18**(11):1081—8.
4. Bonten MJ. Healthcare epidemiology: ventilator-associated pneumonia: preventing the inevitable. *Clin Infect Dis* 2011; **52**(1):115—21.
5. Allegranzi B, Bagheri Nejad S, Combescure C, Graafmans W, Attar H, Donaldson L, et al. Burden of endemic health-care-associated infection in developing countries: systematic review and meta-analysis. *Lancet* 2011;**377**(9761):228—41.
6. Erdem H, Dizbay M, Karabey S, Kaya S, Demirdal T, Koksal I, et al. Withdrawal of *Staphylococcus aureus* from intensive care units in Turkey. *Am J Infect Control* 2013;**41**(11):1053—8.
7. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS international sepsis definitions conference. *Crit Care Med* 2003;**31**(4):1250—6.
8. Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. *Clin Microbiol Infect* 2012;**18**(3):268—81.
9. Freeman GH, Halton JH. Note on exact treatment of contingency, goodness of fit and other problems of significance. *Biometrika* 1951;**38**:141—9.
10. Firth P, Ttendo S. Intensive care in low-income countries — a critical need. *N Engl J Med* 2012;**367**(21):1974—6.
11. Erdem H, Kurtaran B, Arun O, Yilmaz H, Celebi G, Ozkaya HD, et al. The place and the efficacy of infectious disease consultations in the hospitals. *Infect Dis Clin Pract* 2012;**20**:131—6.
12. McGahan M, Kucharski G, Coyer F. Nurse staffing levels and the incidence of mortality and morbidity in the adult intensive care unit: a literature review. *Aust Crit Care* 2012;**25**(2): 64—77.
13. Vincent JL, Bihari DJ, Suter PM, Bruining HA, White J, Nicolas-Chanoin MH, et al. The prevalence of nosocomial infection in intensive care units in Europe. Results of the European Prevalence of Infection in Intensive Care (EPIC) Study. EPIC International Advisory Committee. *J Am Med Assoc* 1995;**274**(8): 639—44.
14. Vincent JL, Rello J, Marshall J, Silva E, Anzueto A, Martin CD, et al. International study of the prevalence and outcomes of infection in intensive care units. *J Am Med Assoc* 2009; **302**(21):2323—9.
15. Pilato F, Profice P, Dileone M, Ranieri F, Capone F, Minicuci G, et al. Stroke in critically ill patients. *Minerva Anestesiol* 2009; **75**(5):245—50.
16. Rubenfeld GD. Interventions to improve long-term outcomes after critical illness. *Curr Opin Crit Care* 2007;**13**(5):476—81.
17. Vardakas KZ, Rafailidis PI, Konstantelias AA, Falagas ME. Predictors of mortality in patients with infections due to multidrug resistant Gram negative bacteria: the study, the patient, the bug or the drug? *J Infect* 2013;**66**(5):401—14.
18. Rosenthal VD, Maki DG, Salomao R, Moreno CA, Mehta Y, Higuera F, et al. Device-associated nosocomial infections in 55 intensive care units of 8 developing countries. *Ann Intern Med* 2006;**145**(8):582—91.
19. Mehta Y, Jaggi N, Rosenthal VD, Rodrigues C, Todi SK, Saini N, et al. Effectiveness of a multidimensional approach for prevention of ventilator-associated pneumonia in 21 adult intensive-care units from 10 cities in India: findings of the International Nosocomial Infection Control Consortium (INICC). *Epidemiol Infect* 2013:1—9.
20. Bukhari SZ, Hussain WM, Banjar AA, Fatani MI, Karima TM, Ashshi AM. Application of ventilator care bundle and its impact on ventilator associated pneumonia incidence rate in the adult intensive care unit. *Saudi Med J* 2012;**33**(3):278—83.
21. Schwaber MJ, Carmeli Y. The effect of antimicrobial resistance on patient outcomes: importance of proper evaluation of appropriate therapy. *Crit Care* 2009;**13**(1):106.
22. Giske CG, Monnet DL, Cars O, Carmeli Y. Clinical and economic impact of common multidrug-resistant gram-negative bacilli. *Antimicrobial Agents Chemother* 2008;**52**(3):813—21.
23. Inan A, Ozgultekin A, Akcay SS, Engin DO, Turan G, Ceran N, et al. Alterations in bacterial spectrum and increasing resistance rates in isolated microorganisms from device-associated infections in an intensive care unit of a teaching hospital in Istanbul (2004—2010). *Jpn J Infect Dis* 2012;**65**(2): 146—51.
24. Pourakbari B, Sadr A, Ashtiani MT, Mamishi S, Dehghani M, Mahmoudi S, et al. Five-year evaluation of the antimicrobial susceptibility patterns of bacteria causing bloodstream infections in Iran. *J Infect Dev Ctries* 2012;**6**(2):120—5.