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CLINICAL AND EPIDEMIOLOGICAL STUDY

Device-associated infections in the intensive care units of Cyprus: results of the first national incidence study

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Abstract
Background Surveillance of healthcare-associated infections (HCAIs) has become an integral part of infection control programs in several countries, especially in the intensive care unit (ICU) setting. In contrast, surveillance data on the epidemiology of ICU-acquired infections in Cyprus are limited. The aim of this study was to assess the risk of ICU-acquired infections and to identify areas for improvement in Cypriot hospitals by comparing observed incidence rates with international benchmarks and by specifying the microbiological and antibiotic resistance profiles of infecting organisms.
Materials and methods An active surveillance protocol was introduced in the ICUs of the four major public hospitals in Cyprus, based on the methodology of the US National Nosocomial Infections Surveillance system.
Results During February to December 2007, 2,692 patients who were hospitalized in ICUs for a mean length of stay of 5 days acquired 214 infections for an overall incidence rate of 15.8 infections per 1,000 patient-days [95% confidence interval (CI): 13.8–18.1]. Bloodstream infections, pneumonias and urinary tract infections accounted for 80.4% of all infections; of these, 87.8% were device-related. Central line-associated bloodstream infection (CL-BSI) posed the greatest risk (18.6 cases per 1,000 central line-days; 95% CI 14.9–22.9), followed by ventilator-associated pneumonia (VAP) (6.4 cases per 1,000 ventilator-days; 95% CI 4.5–8.8) and catheter-associated urinary tract infection (2.8 cases per 1,000 urinary catheter-days; 95% CI 1.9–4.1). Most frequently isolated pathogens included *Pseudomonas aeruginosa* (21.6% of all isolates), coagulase-negative *Staphylococcus* (11.7%), *Enterococcus* spp. (11.3%) and *Staphylococcus aureus* (9.2%). Overall, 29.8% of *P. aeruginosa* isolates were imipenem-resistant and 68.2% of *S. aureus* were methicillin-resistant. The crude excess mortality rate associated with ICU-acquired infections was 33.2% (95% CI 24.9–41.9%) and the mean post-infection stay in the ICUs was 21.6 days (95% CI 17.0–26.2).
Conclusion In comparison to international benchmarks, the markedly high rate of CL-BSI, the high rate of VAP and the resistance patterns of major infecting pathogens identified in this study emphasize the need to improve current practices for appropriate use and management of invasive devices in Cypriot ICUs.

Keywords Healthcare associated infection · Device associated infection · Surveillance · Incidence rate · Intensive care unit · Cyprus

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Introduction

Surveillance of healthcare-associated infections (HCAIs) has become an integral part of infection control programs in several countries, especially in intensive care units (ICUs), where the risk of infection is high [1]. The most widely accepted protocols for surveillance of ICU-acquired infections are those of the National Nosocomial Infections Surveillance (NNIS) system [2, 3], which provides hospitals with ICU type-specific, infection site-specific, device-associated infection rates and device utilization ratios. Such data allow for meaningful intra-unit comparisons of infection rates, thereby stimulating hospitals to optimize their prevention policy to the best practices described in guidelines and employed by their peers [4, 5]. This ability has proven to be a key component in reducing infection risk [6–8].

In contrast, data on the epidemiology of ICU-acquired infections in Cyprus are limited. A recent prevalence survey in Cypriot hospitals showed that the prevalence of patients with ICU-acquired infection (22%) [9] is similar to that reported in the European Prevalence of Infection in Intensive Care Study (21%) [10] and the rate found in more recent studies in European countries, including France (22%), the UK and Wales (23%) and Spain (26%) [11–13]. However, prevalence data are difficult to use for comparisons, because such data make no allowance for adjustment of rates for the most significant risk factor for most ICU-acquired infections—the use of invasive devices.

This study reports the results of the first attempt to introduce an active surveillance system of ICU-acquired infections in the Cypriot public hospitals by implementing a standardized methodology. Our objectives were to assess the risk of ICU-acquired infections and to identify areas for improvement in our region by comparing observed incidence rates with comparable international benchmarks and by specifying the microbiological and antibiotic resistance profiles of infecting organisms.

Methods

Setting

The study was conducted from February to December 2007 in four adult ICUs in Cyprus, as part of the activities of a cross-border project for the establishment of systematic surveillance and control of HCAIs in hospitals in Cyprus and in the region of Crete in Greece. The project was coordinated by the Infection Control Unit of the University Hospital of Heraklion in Crete.

Study ICUs represent all available adult intensive-care beds in the public health services of Cyprus and are located in the four major hospitals in the country. All ICUs care mainly for medical and surgical patients, with a minor mix of other types of patients such as neurosurgical and trauma patients. Hospital infection control in Cyprus is at a developmental stage. Each hospital has an infection control committee comprising an infectious diseases physician, a microbiologist and one infection control nurse. These committees started functioning in 1999 and their activities are coordinated by a central committee in the Ministry of Health. However, there are no national guidelines for the prevention of HCAIs and individual hospitals have adapted guidelines from internationally recognized standards, mainly those issued by the US Centers for Disease Control and Prevention. There is no official body responsible for the control of antibiotic-resistant organisms or the audit of hospital infection control activities. To date no hospital is required to include surveillance as part of their basic infection control program.

Study design and data collection

In this prospective surveillance study, all patients who were admitted to the ICU during the 11-month study period were actively monitored for HCAI at all body sites until their discharge or death. A standardized survey record form was used to collect data for each patient who presented an infection at least 48 h after their admission in the ICU, based on the ICU component protocol of the NNIS system [2, 3]. Data recorded for each infected patient included demographic information, date of onset and site of infection, time and duration of exposure to invasive devices, isolated pathogens, antibiogram results, and outcome on discharge from the ICU. Denominator data were recorded daily at the level of the entire unit, and included the numbers of patients in the ICU, newly admitted patients, patients exposed to invasive devices, patients receiving antibiotics and patients who died in each ICU.

HCAIs were defined according to the latest criteria from the Centers for Disease Control and Prevention [2]. For purposes of analysis, HCAIs were categorized into pneumonias, bloodstream infections, urinary tract infections, and other infections. Bloodstream infections were primary cases, reported when there was no evident infection at another site, and included both laboratory-confirmed infections and clinical sepses. For purposes of comparisons of infection rates with international data, clinical sepses were removed from calculation of bloodstream infection rates when appropriate. Pneumonias included clinically defined cases, cases with specific laboratory findings, and cases in immunocompromised patients [2]. Pneumonia and bloodstream infection were considered to be device-associated if a ventilator or a central line was in place at the time of or within 48 h before the onset of the infection.

Urinary tract infection was defined as catheter-associated if the patient had an indwelling urinary catheter at the time of or within 7 days before the onset of the infection [2, 3].

Up to four pathogens for each infection could be recorded in the survey form. The isolates were identified by conventional methods and antibiotic susceptibility tests were performed according to standard guidelines [14]. Multi-drug resistant organisms were defined as those resistant to two or more classes of antibiotics.

Study data were collected by infection control nurses and physicians who had attended training sessions regarding the study protocol. All cases of HCAI detected in each ICU were discussed and approved during local meetings of the infection control committees. Completed survey forms were submitted to the coordinating centre on a continuous basis through a secure web-based data-entry system. The coordinating centre was responsible for data management, including data checking for obvious errors and omissions, corrective queries, statistical analysis, and feedback of overall results to each participating hospital. Patient confidentiality was protected by coding the data, which could be identified only by the hospital's infection control team.

Statistical analysis

Device and antibiotic use ratios were calculated by dividing the number of days of use by the number of patient-days. Total infection and device-associated infection incidence rates were calculated as the number of infections per 1,000 patient-days and 1,000 device-days, respectively [2, 3]. Confidence intervals (CIs) for incidence rates were calculated using Fisher's exact method. Wilson's Score method was employed to calculate CI for mortality rates and for differences between mortality rates. Mean lengths of stays were compared using the Mann–Whitney test. WinPepi, version 4, was used to carry out the required calculations [15].

Results

Studied population

During the surveillance period, a total of 2,692 patients were admitted to the participating units, for an aggregate of 13,543 patient-days and a mean length of stay of 5.0 days. The overall device use ratios were 0.34 for central lines, 0.44 for ventilators, and 0.71 for urinary catheters. The antibiotic use ratio was 0.56. A total of 296 patients died in the ICU, for a crude mortality rate of 11% (Table 1).

ICU-acquired infection rates

A total of 214 HCAIs were detected in 129 (4.8%) patients during their ICU stays, resulting in an overall infection rate of 15.8 infections per 1,000 patient-days (95% CI 13.8–18.1). Of the total HCAIs, 85 (39.7%) occurred in patients who had already had previous HCAI episodes. Three infection sites represented 80.4% of all infections; bloodstream (103 cases, 48.1%), lungs (40 cases, 18.7%), and urinary tract (29 cases, 13.6%). The vast majority of primary bloodstream infections (99 cases, 96.1%) were laboratory confirmed and most cases of pneumonia were defined according to specific laboratory findings (24 cases, 60.0%).

Most infections at major sites were associated with the use of invasive devices; 86 (83.5%) primary bloodstream infections were associated with central intravenous lines, 38 (95.0%) pneumonias were associated with mechanical ventilation, and 27 (93.1%) urinary tract infections occurred in catheterized patients.

Device-associated infection rates varied among participating ICUs, ranging from 4.1 to 10.2 cases of ventilator-associated pneumonia (VAP) per 1,000 ventilator-days (pooled mean 6.4; 95% CI 4.5–8.8); from 3.7 to 22.9 cases of central line-associated bloodstream infection (CL-BSI) per 1,000 central line-days (pooled mean 18.6; 95% CI: 14.9–22.9); and from 2.0 to 3.3 cases of urinary catheter-associated

Table 1 Features of participating intensive-care units, February to December 2007

Unit	Number of beds	Nurse to patient Ratio[a]	Number of admissions	Patient-days	Mean LOS (days)	Device use ratios			Antibiotic use ratio	Crude mortality (%)
						CL	MV	CA		
A	17	0.7	640	4,929	7.7	0.59	0.64	0.93	0.69	18.0
B	11	0.5	449	3,230	7.2	0.25	0.45	0.67	0.40	9.4
C	11	0.5	766	3,205	4.2	0.21	0.31	0.61	0.54	13.6
D	8	2.0	837	2,179	2.6	0.12	0.15	0.39	0.56	4.2
Total	47	0.8	2,692	13,543	5.0	0.34	0.44	0.71	0.56	11.0

LOS length of stay, *CL* central lines, *MV* mechanical ventilation, *CA* urinary catheter

[a] Per 24 h

urinary tract infection (CA-UTI) per 1,000 catheter-days (pooled mean 2.8; 95% CI 1.9–4.1). Excluding clinical sepsis, the overall rate of laboratory confirmed CL-BSI was 17.9 cases per 1,000 central line-days (95% CI 14.3–22.2).

Microbiology data

One hundred and ninety-seven (92.1%) of the recorded ICU-acquired infections were culture positive. Of these, 71 (36.0%) were polymicrobial. Of the 283 bacterial strains isolated, 157 (55.5%) were Gram-negative microorganisms, 97 (34.3%) were Gram-positive microorganisms, 26 (9.2%) fungi, and 3 (1.1%) were anaerobes. The four most frequently isolated pathogens were *Pseudomonas aeruginosa* (21.6% of all isolates), coagulase-negative *Staphylococcus* (11.7%), *Enterococcus* spp. (11.3%) and *Staphylococcus aureus* (9.2%). The distribution of pathogens by site of infection is presented in Table 2. Results of antibiotic susceptibility tests are provided in Table 3. Overall, 34.4% of *P. aeruginosa*, 56.3% of *Acinetobacter baumannii* and 20.9% of *Enterobacteriaceae* isolates were multi-drug resistant.

Impact on patient outcomes

The crude ICU-mortality rate was significantly higher for patients who acquired an infection (55/129, 42.6%) than those without an ICU-acquired infection (241/2,563, 9.4%), yielding an overall crude excess mortality rate of 33.2% (95% CI 24.9–41.9%). Mortality in the ICUs reached 50.0% for patients who had multiple infections at different sites, while for those with single-site infections mortality rates varied according to the site of infection: 45.5% for bloodstream infection, 43.5% for pneumonia, 27.3% for urinary tract infection, and 23.1% for infection at another site.

The mean length of stay after an episode of infection in the ICU was 21.6 days (95% CI 17.0–26.2 days) and varied by site of infection: 31.6 days for patients with multiple-site infections, 19.8 days for those with bloodstream infection, 16.3 days for pneumonia, 15.5 days for urinary tract infection, and 12.6 days for patients with other single-site infections. Mean post-infection stay was significantly higher for patients who had a device-associated infection than those with a non-device related infection (24.0 vs. 11.4 days, $p = 0.007$).

Table 2 Distribution of isolates recovered from patients with intensive-care unit-acquired infections in Cyprus, February to December 2007

Pathogen, by class	Percentage of isolates, by type of infection			
	UTI ($n = 36$)	BSI ($n = 140$)	PNEU ($n = 44$)	Other ($n = 63$)
Gram-positive				
Enterococcus spp.	13.9	13.6	2.3	11.1
Staphylococcus aureus	0.0	9.3	15.9	9.5
Coagulase-negative *Staphylococcus*	2.8	18.6	6.8	4.8
Other	2.8	2.1	0.0	3.2
Enterobacteriaceae				
Escherichia coli	19.4	2.9	2.3	4.8
Klebsiella spp.	2.8	7.9	2.3	7.9
Serratia marcescens	2.8	6.4	0.0	11.1
Enterobacter clocae	2.8	4.3	0.0	0.0
Other	2.8	3.6	2.3	4.8
Other Gram-negative bacilli				
Pseudomonas aeruginosa	30.6	17.1	29.5	20.6
Acinetobacter baumannii	5.6	3.6	11.4	6.3
Stenotrophomonas maltophilia	2.8	2.9	4.5	0.0
Other	2.8	1.4	0.0	4.8
Fungi				
Candida spp.	8.3	5.0	20.5	7.9
Other	0.0	0.7	2.3	0.0
Anaerobic bacilli	0.0	0.7	0.0	3.2

UTI urinary tract infection, *BSI* bloodstream infection, *PNEU* pneumonia, *Other* infection at other site

Table 3 Antibiotic resistance patterns of the most frequent pathogens associated with intensive care unit-acquired infections in Cyprus, February to December 2007

Pathogen	Antibiotic	No. of isolates tested/total	No. (%) of resistant isolates
Staphylococcus aureus	Methicillin	22/26	15 (68.2)
Coagulase-negative *Staphylococcus*	Methicillin	30/33	26 (86.7)
Enterococcus spp.	Vancomycin	29/32	1 (3.4)
Pseudomonas aeruginosa	Ciprofloxacin	61/61	22 (36.1)
	Ceftazidime	58/61	15 (25.9)
	Piperacillin and tazobactam	45/61	19 (42.2)
	Imipenem	57/61	17 (29.8)
Acinetobacter baumannii	Ciprofloxacin	14/16	8 (57.1)
	Ceftazidime	15/16	9 (60.0)
	Piperacillin and tazobactam	9/16	1 (11.1)
	Imipenem	10/16	0 (0.0)
Enterobacteriaceae	Ciprofloxacin	67/67	16 (23.9)
	Ceftazidime	64/67	15 (23.4)
	Imipenem	67/67	0 (0.0)

Discussion

This is the first prospective surveillance study to investigate the magnitude and nature of the problem of ICU-acquired infections in Cyprus. Our overall rate of 15.8 HCAIs per 1,000 patient-days appears to be similar to or lower than that reported in international studies [16–19], but our findings also suggest that these infections had a major contribution to mortality and prolongation of stay of patients in participating ICUs.

Both the urinary catheter utilization ratio and the CA-UTI rate in this study (0.71 and 2.8, respectively) closely resemble the mean values reported by the medical-surgical adult ICUs in non-teaching hospitals participating in the US National Healthcare Safety System (NHSN) (0.72 and 3.1, respectively) [20]. Comparable CA-UTI rates have been reported in medical-surgical ICUs in Germany and Greece (3.1 and 3.5 cases per 1,000 catheter-days, respectively) [17, 21], while similar studies in other European countries have reported higher rates [18, 22].

The overall VAP rate in this study (6.4 cases per 1,000 ventilator-days) appears to be lower than the rates reported in mixed ICUs in other European countries [7, 17, 18, 23, 24], but this difference probably reflects the use of a different case definition [2]. However, data from the NHSN are appropriate for comparison with the present study [20]. Our ventilator use ratio is equal to that reported in NHSN medical-surgical ICUs in teaching hospitals (0.44), but our VAP rate is higher [6.4 (95% CI 4.5–8.8) vs. 3.3 (95% CI 3.1–3.6) cases per 1,000 ventilator-days, respectively]. This difference from the NHSN data might be partly explained by different case-mix, but it is large enough to assume to also represent infection control shortcomings in our ICUs. Moreover, the wide disparity of VAP rates observed in individual ICUs in this study, even after adjusting for exposure to ventilators, may reflect variable efficiency in VAP prevention practices across ICUs and indicates a reduction potential in our region.

The central line use ratio in our ICUs is low compared with that in NHSN medical-surgical ICUs (0.34 vs. 0.46–0.59, respectively), but our rate of laboratory-confirmed CL-BSI is markedly higher (17.9 vs. 1.5–2.0 cases per 1,000 catheter-days) [20]. Similar conclusions hold when our results are compared with data from mixed ICUs in Germany and Italy (central line use ratios: 0.69 and 0.97; CL-BSI rates: 1.8 and 3.2, respectively) [7, 23]. These comparisons with external benchmarks emphasize the need to improve current practices in Cypriot ICUs for the management of central venous catheters.

Compared with data from US and European ICUs [16, 25], the proportion of isolation of *P. aeruginosa* was especially high in this study. This finding deserves further investigation in our ICUs, because *P. aeruginosa* is common in the environment and may consequently indicate problems in hand hygiene practices and in cleaning and disinfection procedures used for the respiratory equipment. Also unexpectedly high was the proportion of isolation of *Candida* species in pneumonia cases in this study. However, *Candida* infrequently causes pneumonia [2] and our finding may thus reflect problems in diagnosis or surveillance methodology [26].

Concurrent with other studies showing hyperendemic levels of methicillin-resistant *S. aureus* from routine blood cultures in Cypriot hospitals [27], this study noted a high proportion (68.2%) of methicillin resistance in *S. aureus* isolates implicated in ICU-acquired infections. High rates

of methicillin resistance have also been reported for *S. aureus* isolates implicated in device-associated infections in US hospitals (56.2%) [28] and bloodstream infections in European ICUs (45.8%) [25]. In contrast, vancomycin resistance among enterococci was infrequent in our study (3.4%) and much lower than that found in US hospitals (33.3%) [28]. Therefore vancomycin remains a first line agent for empirical treatment of staphylococcal and enterococcal infections in our region.

A high proportion of resistance to imipenem among *P. aeruginosa* isolates was recorded (29.8%) in this study, but none of the *A. baummanni* and *Enterobacteriaceae* pathogenic isolates was resistant to imipenem. A similar resistance pattern for *Enterobacteriaceae* pathogenic isolates has been described in US hospitals prior to 2004, but according to recent data carbapenem resistance is high for *P. aeruginosa* (25.3%), emerging for *K. pneumoniae* (3.6–10.8%, varying by infection site), and low for *E. coli* (0.9–4.0%) [28]. Therefore, awareness for potential emergence of carbapenem resistance in *Enterobacteriaceae* may also be needed in our region, including the incorporation of the latest guidelines to test for the presence of carbapenemases in carbapenem-susceptible *Enterobacteriaceae* [29]. Moreover, the high rate of imipenem resistance in *P. aeruginosa* indicates that colistin should be included in routine antibiogram tests in Cypriot hospitals. Our results also suggest that imipenem remains active against most of the Gram-negative pathogens in our region and colistin should be reserved only for cases of pseudomonas infection suspicion.

The present study has certain limitations, mainly resulting from the practical compromises necessary in a surveillance system. First, resource constraints did not allow us to conduct an external validation assessment of case-findings in our surveillance system. Second, we relied on each hospital's laboratory for identifying infecting pathogens and their resistance patterns, which may vary in level of expertise and resource availability. Finally, our surveillance protocol did not involve the collection of data on patient's intrinsic and extrinsic risk factors, apart from device use. It is therefore possible that other unmeasured factors may have affected infection rates in this study. This may be especially true for mortality rates, and the crude excess mortality reported in this study may not indicate mortality attributable to infections. However, assessment of risk factors for ICU-acquired infections other than device use and evaluation of the cost-effectiveness of incorporating more elaborate data collection in a surveillance system remain unresolved issues [16, 21, 25].

In conclusion, the markedly high rate of CL-BSI, the high rate of VAP and the resistance patterns of major infecting pathogens identified in this study in comparison to international benchmarks, emphasize the need to review and improve current practices for appropriate use and management of invasive devices in Cypriot ICUs. Establishment of active surveillance programs could further contribute to reducing the burden of ICU-acquired infections in Cyprus.

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Conflict of interest statement None.

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