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Article

Device-Associated Infections in Adult Intensive Care Units: A Prospective Surveillance Study

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Abstract: Device-associated infections (DAIs) are a significant public health concern because of their attributable mortality, along with extra length of stay and cost. This two- year prospective, surveillance study aimed to assess the incidence of DAIs and their clinical impact on 4 Greek adult medical-surgical ICUs. Centers for Disease Control and Prevention (CDC) definitions were used to diagnose DAIs. Of the 500 patients hospitalized for 12,624 days, 254 (50.8%) experienced 346 episodes of DAIs. The incidence of DAIs was 27.4/1,000 bed-days. The incidence of ventilator-associated events (VAEs), central line-associated bloodstream infections (CLABSIs), and catheter-associated urinary tract infections (CAUTIs) was 20.5/1,000 ventilator-days, 8.6/1,000 central-line days and 2.5/1,000 catheter-days, respectively. The most common pathogen isolated was *Acinetobacter baumannii* (35.7%%) and *Klebsiella pneumoniae* (29.9%). All gram-negative pathogens were carbapenem-resistant. DAIs attributable mortality was 20.1% (p = 0.000), while attributable length of stay was 18.9 days (p = 0.000), respectively. The high incidence and attributable length of stay and mortality of DAIs emphasize the need to establish an organized infection surveillance program and implement a care bundle for DAIs prevention in ICUs.

Keywords: device-associated infections; healthcare-associated infections; intensive care units; surveillance; length of stay; mortality

1. Introduction

Healthcare-associated infections (HCAIs) are one of the most serious patient safety issues in healthcare settings, affecting over 1.4 million people worldwide [1]. Patients in intensive care units (ICUs) are at higher risk for HCAIs due to the high prevalence of invasive devices and procedures, induced immunosuppression, comorbidity, frailty and increased age [2].

According to the Centers for Disease Control and Prevention (CDC), the COVID-19 pandemic has had a negative impact on the incidence of HCAIs, with a substantial increase in central line-associated bloodstream infections (CLABSIs), ventilator-associated events (VAEs) and catheter-associated urinary tract infections (CAUTIs) rates recorded through 2020 [3]. Similarly, the International Nosocomial Infection Control Consortium (INICC) study found significant increases in overall mortality, mean length of stay, CLAB- SIs and VAEs rates in ICU in low- and middle-income countries [4].

HCAIs are associated with prolonged hospital stays, long-term disability, increased antimicrobial resistance, a huge additional financial burden on health systems, high costs for patients and their families, and additional deaths [5,6]. Notably, according to studies conducted in high-

income countries, device-associated infections (DAIs), such as CLAB- SIs and VAEs, have a more serious impact than other HCAIs [7]. Of the approximately 250,000 CLABSIs that occur each year in the United States, approximately 28,000 result in death in the ICU, with an annual cost of up to \$2.3 billion [8]. Furthermore, in a study conducted in four European countries, the attributable length of stay per CLABSI episode ranged between 4 and 14 days [9]. The attributable cost per CLABSI episode ranged from €4,200 to €13,030, with the annual cost to healthcare systems ranging between €53.9 million in the UK and €130 million in France [10]. For VAEs, the attributable mortality was estimated between 7% and 30% and the attributable cost between €3,227 and \$6,775 per case [11,12]. For CAUTIs, mortality ranges between 3 and 28%, length of stay is 0.5 to 2.5 days, and costs range from \$876 to \$10,197 per episode [13,14].

This prospective, observational study aimed to assess DAIs rates, microbiological profile and DAIs attributable mortality and length of stay in ICUs patients in Athens, Greece.

2. Materials and Methods

2.1. Research Design

A prospective surveillance was conducted in four medical-surgical ICUs in Athens for a two-year period. The sample consisted of all adult patients hospitalized in the ICUs for more than 2 days during the surveillance period. The nurse to patient ratio was 1 to 3. In all four ICUs, hematological tests were performed daily, chest X-rays were performed 2-4 times per week, and blood, bronchial secretions, urine, or wound cultures were per- formed when clinically indicated. Patients were actively monitored from admission to discharge from the ICU or until death. Exclusion criteria from the study were age under 18 years and ICUs length of stay less than 3 days.

Standard definitions from the CDC's National Healthcare Safety Network were used to diagnose VAEs, CLABSIs, and CAUTIS [15]. There are three levels of definition of VAEs: 1. Ventilator-Associated Conditions (VACs), when respiratory deterioration meets certain criteria for the detection of hypoxemia defined as an increase in daily minimum PEEP \geq 3 cm H2O or FiO2 \geq 0.20 maintained for at least 2 calendar days after a baseline period (2 calendar days) of stability or improvement, 2. Infections attributed to ventilator- associated conditions (IVACs), if considering the above and the presence of general signs of infection/inflammation, defined as a white blood cell count \geq 12,000 cells/mm³ or \leq 4,000 cells/mm³ and/or temperature > 38 °C or < 36 °C, a new antimicrobial agent has been started and continues for at least 4 calendar days and 3. Possible Ventilator-Associated Pneumonia (PVAP), if in addition to the above, there is microbiological confirmation of a lower respiratory tract infection, defined as: purulent respiratory secretions or positive culture (qualitative, semiquantitative or quantitative) or more stringent microbiological criteria, where purulent secretions plus quantitative criteria are mandatory in addition to positive lung histopathology, positive pleural fluid culture and other tests such as *Le-gionella spp*. [15].

The definition of CLABSIs refers to laboratory-confirmed bacteremia in which a selected pathogen that meets the criteria for bacteremia has been isolated and a central line, which has been in place for more than two calendar days, is present on the day of the event or the previous day [15].

To define CAUTIs, the patient must have had an indwelling urinary catheter for more than 2 days on the day of the event and the catheter must be present on the day of the event or removed the day before the event and have at least 1 of the following signs or symptoms: fever (> 38°C), suprapubic tenderness, pain or tenderness in the costovertebral angle with no other recognized cause, increased urinary frequency, urgency, dysuria, and a positive urine culture with $\ge 10^5$ colonies/mL without more than 2 species of organisms isolated and at least one of which is bacterial. The symptoms of increased urinary fre- quency, urgency, and dysuria cannot be used when the catheter is in place [15].

Data were collected daily from patient records, nursing staff forms, and the micro-biological laboratory. The data collected included patient demographics, severity of dis- ease at admission, as indicated by the Acute Physiology and Chronic Health Evaluation (APACHE) II score [16], comorbidities, as indicated by the Charlson Comorbidity Index [17], the type of DAIs (CLABSIS,

VAEs, CAUTIs), duration of exposure to invasive de-vices, pathogens isolated, and patient outcome (discharge or death in ICUs).

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the hospital Ethics Committee. Written informed consent was obtained from all the patients before their participation in this study.

2.2. DAIs Rates

During the surveillance period, the incidence-density of DAIs was calculated. The incidence of VAEs was obtained by dividing the number of VAEs by the number of days on the ventilator and multiplying by 1,000. The incidence of CLABSIs was obtained by dividing the number of CLABSIs by the number of days with a central line and multiplying by 1,000. The incidence of CAUTIs was obtained by dividing the number of CAUTIs by the number of days with a bladder catheter and multiplying by 1,000 [15].

The device utilization ratio was calculated by dividing the number of days with a device by the number of days in ICUs and multiplying by 100. The number of days with a device is the total number of days of exposure to each device (ventilator, central line, bladder catheter) for all patients during the surveillance period. The number of days in ICUs is the total number of days of hospitalization of patients in the ICU during the surveillance period [15].

2.3. Crude Excess Mortality and Length of Stay

To estimate extra mortality and length of stay, comparisons were made between patients with DAIs and patients admitted without HCAIs and who did not develop DAIs during their ICUs stay. Crude excess mortality was defined as the difference between the mortality of patients with DAIs and the mortality of patients without DAIs, while crude excess length of stay was defined as the difference between the mean length of stay of patients with DAIs and the mean length of stay of patients without DAIs.

2.4. Statistical Analysis

Categorical variables were expressed as absolute (N) and relative frequencies (%) and differences between the two groups were compared using the $\chi 2$ test or Fisher exact test, where appropriate. Continuous variables were expressed as median and interquartile range and differences between groups were compared using the non-parametric Mann- Whitney U-test. The Kolmogorov-Smirnov test was used to test for normality. Data analysis was performed using the IBM SPSS Statistics package, version 22.0 and EpiInfo, version 6.04b. All tests were two-sided and statistical significance was defined as p < 0.05, with a power of 95%.

3. Results

During the two-year study period, 500 patients were hospitalized for at least three days in four Greek medical-surgical ICUs for 12,624 ICUs days. 254 (50.8%) of the 500 patients developed 346 DAIs episodes in ICUs. Table 1 shows the distribution of demo- graphic and clinical characteristics studied in patients with and without DAIs. Medical admission category was more frequent in patients with DAIs (p = 0.003), who had a higher APACHE II score at ICUs admission (p = 0.004), compared to patients without DAIs. In patients with DAIs, infection was a more frequent reason for ICUs admission compared to patients without DAIs (p = 0.022), who were admitted more often due to post operative monitoring (p = 0.000). Patients with DAIs had significantly longer ICU length of stay (29 days versus 11 days, p = 0.000), central line (29 days versus 11 days, p = 0.000) and urinary catheter (29 days versus 11 days, p = 0.000), compared to patients without DAIs. Also, patients with DAIs received antibiotics for more days, compared to patients without DAIs (28 days versus 10 days, p = 0.000) (Table 1).

Table 1. Characteristics of patients with and without device-associated infections.

Variable	All (n=500)	DAIs (n= 254)	No DAIs (n= 246)	Pvalue
Male sex, n (%)	297 (59.4)	160 (63)	137 (55.7)	0.102
Age, median (interquartile range)	61.5 (47-74)	61.5 (47-74)	61.5 (46.7-75.2)	0.813
Admission category, n (%)				
Medical	300 (60)	169 (66.5)	131 (53.3)	0.003
Surgical	200 (40)	85 (33.5)	115 (46.7)	
Reason for ICU admission, n (%)				
Infection	122 (24.4)	73 (28.7)	49 (19.9)	0.022
Post operative monitoring	87 (17.4)	23 (9.1)	64 (26)	0.000
Trauma	83 (16.6)	49 (19.3)	34 (13.8)	0.118
Neurological disease	72 (14.4)	38 (15)	34 (13.8)	0.799
Pulmonary disease	68 (13.6)	42 (16.5)	26 (10.6)	0.067
Cardiovascular disease	36 (7.2)	16 (6.3)	20 (8.1)	0.490
Malignancy	22 (4.4)	8 (3.1)	14 (5.7)	0.194
Other (burn, poisoning)	10 (2.2)	5 (2)	5 (2)	1.000
APACHE II score, median	18 (15-21)	19 (15-22)	17 (14-21)	0.004
(interquartile range)				
Charlson comorbidity index, median	3 (1-5)	3 (1-5)	3 (1-5)	0.279
(interquartile range)				
Invasive procedures, n (%)				
Central venous catheter	500 (100)	254 (100)	246 (100)	NA
Urinary catheter	500 (100)	254 (100)	246 (100)	NA
Endotracheal tube	500 (100)	254 (100)	246 (100)	NA
Tracheostomy	182 (36.4)	130 (51.2)	52 (21.1)	0.000
Tube thoracostomy	39 (7.8)	21 (8.3)	18 (7.3)	0.741
Hemodialysis	131 (26.2)	58 (22.8)	73 (29.7)	0.085
Days in ICU, median (interquartile	19 (10-32)	29 (20-44)	11 (7-19)	0.000
range)				
Days of mechanical ventilation,	15 (7-27)	23 (15-35.2)	8 (5-15)	0.000
median (interquartile range)				
Days with central line, median	19 (10-	29 (19-44.2)	11 (7-19)	0.000
(interquartile range)	32.7)			
Days with urinary catheter, median	19 (10-	29 (20-46.2)	11 (7-19)	0.000
(interquartile range)	34)			
Days with antibiotics, median	17 (9-30)	28 (17-42)	10 (6-16)	0.000
(interquartile range)				

DAIs = Device-Associated Infections; ICU = Intensive Care Unit; NA = Not applicable.

The overall rate of DAIs was 27.4 episodes per 1,000 ICUs days (95% CI, 24.6-30.4). Table 2 shows DAIs rates by infection types. VAEs were the most common type of DAIs, with an incidence of 20.5 episodes per 1,000 ventilator-days, followed by CLABSIs, with 8.6 episodes per 1,000 central line-days and CAUTIs, with 2.5 episodes per 1000 catheter- days. Of the 207 VAEs episodes, the majority were VACs (51.2%), followed by IVACs with a rate of 31.4% and PVAPs with a rate of 17.4%. The device utilization ratio was 80.1% for mechanical ventilation, 99.6% for central catheters, and 100% for urinary catheters (Table 2).

Table 2. Device-associated infections rates.

Type of DAIs	No of	Device	Device	No of infections	DAIs rates (95%
	bed	days	utilization		CI)
	days		ratio		
VAEs	12624	10112	80.1%	207	20.5 (17.8-23.4)
VACs	12624	10112	80.1%	106	10.5 (8.6-12.6)
IVACs	12624	10112	80.1%	65	6.4 (5.0-8.1)
PVAPs	12624	10112	80.1%	36	3.6 (2.5-4.9)
CLABSIs	12624	12568	99.6%	108	8.6 (7.1-10.3)
CAUTIs	12624	12624	100%	31	2.5 (1.7-3.4)

DAIs = Device-Associated Infections; VAEs = Ventilator-Associated Events; VACs = Ventilator-Associated Conditions; IVACs = Infections attributed to ventilator-associated conditions; PVAPs = Possible Ventilator-Associated Pneumonia; CLABSIs = Central Line-Associated Bloodstream Infections; CAUTIs = Catheter-Associated Urinary Tract Infections; CI = Confidence Intervals.

The median (IQR) time from the start of ventilation to the onset of VAEs was 7 (4-14) days. The median (IQR) time from the central line insertion to the onset of CLA-BSIs was 7 (5-10) days, while the median (IQR) time from the urinary catheter insertion to the onset of CAUTIs was 10 (5-15) days, respectively.

The distribution of pathogens by type of DAIs varied. 56 (16.2%) of the 346 DAIs were polymicrobial. The most common pathogens isolated were *Acinetobacter baumannii* (35.7%), *Klebsiella pneumoniae* (29.9%) and *Pseudomonas aeruginosa* (19.5%). *Acinetobacter baumannii* was the most common pathogen isolated in patients with VAEs (44.4%) and in patients with CLABSIs (44.4%), and *Klebsiella pneumoniae* was the most common pathogen isolated in patients with CAUTIs (48.4%). Overall, 100% of *Acinetobacter baumannii*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* were carbapenem-resistant.

Table 3 shows the impact of DAIs in ICUs mortality. The ICUs mortality was 44.9% for patients who acquired a DAI and 24.8% for patients without a DAI, yielding an overall crude extra mortality of 20.1% (p = 0.000). The ICUs mortality rates for patients with VAEs, CLABSIs and both VAEs and CLABSIs were significantly higher than the mortality rate for patients without DAIs, yielding crude extra mortality rates of 22.1% (p = 0.000), 20.6% (p = 0.012) and 25.2% (p = 0.011), respectively (Table 3).

Table 3. Device-associated infections attributable mortality.

Type of DAIs	No of deaths	Mortality (%)	Crude extra	Pvalue
			mortality (%)	
None	61	24.8	-	-
DAIs	114	44.9	20.1	0.000
VAEs	97	46.9	22.1	0.000
CLABSIs	49	45.4	20.6	0.012
CAUTIs	14	45.2	20.4	0.245
VAEs and CLABSIs	32	50	25.2	0.011
VAEs and CAUTIs	11	47.8	23	0.188
CLABSIs and CAUTIS	6	42.9	18.1	0.575
VAEs, CLABSIs and CAUTIs	3	37.5	12.7	1.000

DAIs = Device-Associated Infections; VAEs = Ventilator-Associated Events; CLABSIs = Central Line-Associated Bloodstream Infections; CAUTIs = Catheter-Associated Urinary Tract Infections.

Table 4 provides data on ICUs length of stay in patients hospitalized during the surveillance period, without DAIs and with DAIs. The mean ICUs length of stay was 34.5 days for patients who acquired a DAI and 15.6 days for patients without a DAI, yielding a crude extra length of stay of 18.9 days (p = 0.000). The extra length of stay for patients with VAEs, CLABSIs and CAUTIs was 19, 24.1 and 38.5 days (p = 0.000), respectively. In patients with more than one DAIs the crude extra length of stay ranges between 27.2 and 51.4 days (p = 0.000) (Table 4).

Type of DAIs Mean length of stay, Pvalue Crude extra length days of stay, days None 15.6 **DAIs** 34.5 18.9 0.000 VAEs 34.6 19 0.000 **CLABSIs** 39.7 24.1 0.000 **CAUTIS** 54.1 38.5 0.000 27.2 VAEs and CLABSIs 42.8 0.000 VAEs and CAUTIS 54.1 38.5 0.000 CLABSIs and CAUTIS 66.4 50.8 0.000 0.000 VAEs, CLABSIs and CAUTIs 67 51.4

Table 4. Device-associated infections attributable length of stay.

 $DAIs = Device-Associated \ Infections; \ VAEs = Ventilator-Associated \ Events; \ CLABSIs = Central \ Line-Associated \ Bloodstream \ Infections; \ CAUTIs = Catheter-Associated \ Urinary \ Tract \ Infections.$

4. Discussion

Our results highlight the serious problem of DAIs in Greek ICUs, since approximately 50% of patients experienced at least one episode of DAI, with an incidence-density of 27.4 DAIs per 1,000 bed-days. The frequency of DAIs was significantly higher, compared to the United States CDC's National Healthcare Safety Network (NHSN) report (0.9-4.4 DAIs per 1,000 bed-days) and the INCC reports from 45 countries (9.0-10.1 DAIs per 1,000 bed-days) [1,18,19]. There are some reasons that could explain this difference, such as the socio-economic level of the country, the lack of an organized surveillance system, the reduced resources for infection prevention and control and the low compliance with infection prevention measures [20–22].

Device utilization ratio constitutes a necessary measurement when combined with the measurement of DAIs rates due to its important role in the HCAIs surveillance process. Measuring the device utilization ratio can provide information on the risk of device-associated events, such as CLABSIs, VAEs and CAUTIS [23]. Device utilization ratios were found to be 80.1%, 99.6%, and 100% for mechanical ventilation, central lines, and urinary catheters, respectively. Notably, all the device utilization ratios in this investigation were higher than those reported by the NHSN for the year 2013 [1], as well as higher than data reported by the INICC for the periods 2013-2018 (37.4%, 51.1% and 58.7%, respectively) [18] and 2015-2020 (43%, 63% and 67%, respectively) [19]. The elevated rates of DAIs may indicate the increased utilization of devices. The frequency of DAIs increases with the duration of device use. Additionally, the device use may increase the risk for the colonization of multidrug-resistant pathogens. Achieving equilibrium between effective device usage and infection control protocols is essential for minimizing the risk of DAIs and resistant micro-organisms colonization [23–25].

The most common pathogens isolated in the 4 ICUs were *Acinetobacter baumannii* and *Klebsiella pneumoniae*. Our results agree with a previous systematic review published in 2022 [26]. Prospective studies show that the rates of gram-negative pathogens resistant to carbapenems have increased in Europe [27]. In Greece, the frequency of carbapenem-resistant *Acinetobacter baumannii* strains reaches 98%, followed by *Klebsiella pneumoniae* strains with a rate of 75% and *Pseudomonas aeruginosa* strains with a rate of 46%, respectively [28]. The resistance rates in our study were 100%, highlighting the

endemic situation prevailing in Greek ICUs. The presence of multidrug-resistant pathogens can be attributed to the lack of appropriate policies regarding antibiotic use in most Greek hospitals. More efforts are needed to adopt antimicrobial stewardship, to prevent and control DAIs and antimicrobial resistance in Greek ICUs [29].

Also, this study presents data on the clinical impact of DAIs on ICU mortality rates and length of stay during the surveillance period. From our results it seems that DAIs acquisition increase ICU mortality approximately 2 times. If the patient presents 2 or 3 DAIs simultaneously, the extra mortality increases more significantly, reaching over 25%. Also, the mean length of stay increased 2 times when DAI was present, while in patients with 2 or 3 DAIs simultaneously, it is increased 3 to 4 times, compared to patients without DAIs. Our results are confirmed by previous multi-center surveillance studies, which report that DAIs increase mortality and length of stay in adult and pediatric ICUs [18,19]. However, it is important to note that we did not proceed with further analysis of our data in order to identify if DAIs are an independent risk factor for ICU mortality and length of stay, after adjusting by several other variables. Nevertheless, other researchers have demonstrated that some unlikely to change risk factors are: country income-level, hospitalization type, sex, and age, while some modifiable risk factors are: DAIs, length of stay and device utilization ratio [19,30–32]. Additionally, low nurse-to-patient ratios have been identified as barriers for infection prevention and control [33–35]. In each of the 4 ICUs, the nurse-to-patient ratio was 1:3. Although there are several risk factors for the occurrence of DAIs, suboptimal nurse staffing levels may be a barrier to its elimination in ICUs [33-35]. The high crude attributable mortality rates of DAIs emphasize the implementation of active outcome surveillance programs and procedures to identify patients at risk, as well as to identify gaps in DAIs control practice, provide staff feedback, and target performance improvement activities that will contribute to the reduction of DAIs.

Our results should be interpreted in the context of some potential limitations. First, as the present study was conducted in four ICUs in Athens, our sample may not represent the typical characteristics of patients in other ICUs in our country, which likely affects the rates of DAIs and attributable mortality. Second, due to the study design, we may not have considered some potential confounding factors, which could have affected the magnitude of our findings. For example, critically ill patients are more likely to remain in the ICUs for prolonged periods and to die due to the severity of their illness rather than due to DAIs. In addition, it is important to emphasize that the present research was conducted from a hospital perspective. The consequences of mortality related to DAIs from a societal perspective (e.g., loss of productivity) were not considered. Due to this perspective, the time horizon of the analysis is limited to the ICUs period. However, DAIs impose a significant burden in other settings as well. After discharge from the ICUs, patients are transferred to hospital clinics. Further analysis could therefore be considered to extend this perspective beyond the ICUs.

Despite limitations, this study presents an accurate mapping of the incidence of DAIs, based on CDC's standard definitions and protocols for diagnosing DAIs and monitoring ICUs patients [15].

5. Conclusions

Our findings highlight the significance of monitoring DAIs in ICUs patients. The elevated prevalence of DAIs, the frequency of device usage, and the levels of antimicrobial resistance among the pathogens found in this study, emphasize the need for establishing an organized infection control and prevention program, which can minimize the impact of DAIs, enhancing the ICUs patient safety and quality of care.

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Data Availability Statement: The data presented in this study are available on reasonable request from the corresponding author.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

APACHE Acute Physiology and Chronic Health Evaluation
CAUTIS Catheter-Associated Urinary Tract Infections
CDC Centers for Disease Control and Prevention
CLABSIS Central Line-Associated Bloodstream Infections

DAIs Device-Associated Infections HCAIs Healthcare-Associated Infections

ICUs Intensive Care Units

IVACs Infections Attributed to Ventilator-Associated Conditions INICC International Nosocomial Infection Control Consortium

NHSN National Healthcare Safety Network PVAP Possible Ventilator-Associated Pneumonia

VACs Ventilator-Associated Conditions VAEs Ventilator-Associated Events

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