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Incidence and risk factors of device-associated infections and associated mortality at the intensive care in the Dutch surveillance system

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Abstract *Objective:* To examine the incidence of and risk factors for device-associated infections and associated mortality. *Design and setting:* Prospective surveillance-based study in ICUs of 19 hospitals in The Netherlands. *Patients:* The study included 2,644 patients without infection at admission during 1997–2000, staying in the ICU for at least 48 h. *Measurements and results:* The occurrence of ventilator-associated pneumonia (VAP), central venous catheter (CVC) related bloodstream infection (CR-BSI), urinary catheter-associated urinary tract infection (CA-UTI) and risk factors was monitored. Of the ventilated patients 19% developed pneumonia (25/1,000 ventilator days); of those with a central line 3% developed CR-BSI (4/1,000 CVC days,) and of catheterized patients 8% developed CA-UTI (9/1,000 catheter days). Longer device use increased the risk for all infections, especially for CR-BSI. Independent risk factors were sex, immunity, acute/elective admission, selective decontamination of the digestive tract, and systemic antibiotics at admission, dependent upon the infection type. Crude mortality significantly differed in patients with and without CR-BSI (31% vs. 20%) and CA-UTI (27% vs. 17%) but not for VAP (26% vs. 23%). Acquiring a device-associated infection was not an independent risk factor for mortality. Being in need of ventilation or a central line, and the duration of this, contributed significantly to mortality, after adjusting for other risk factors. *Conclusions:* Device use was the major risk factor for acquiring VAP, CR-BSI and CA-UTI. Acquiring a device-associated infection was not an independent risk factor for mortality, but device use in itself was.

Keywords Nosocomial infections · Intensive care unit · Device use · Risk factors · Mortality · Incidence

Introduction

Information on the incidence of different intensive care unit (ICU) acquired infections and their risk factors can help clinicians, other healthcare workers, and hospital policy makers to try to reduce the burden of ICU-acquired infections in patients. This will not only lead to less suffering but may also be cost saving. In a European prevalence survey in which 78 ICUs in The Netherlands participated 16% of the Dutch patients had an ICU-acquired infection [1]. In The Netherlands PREZIES, a national network, started a surveillance of nosocomial infections at the ICU in 1997 which continued until the end of 2000. As in most European surveillance systems, the definitions used were based on those of the Centers for Disease Control (CDC)/National Nosocomial Infections Surveillance (NNIS) system. However, unlike the surveillance in the United States [2] and Germany [3], this surveillance is patient based instead of unit based. The infection rates have been previously reported to the participating hospitals, in a Dutch journal [4], and in abstract form [5]. All ICU-acquired infections were recorded, but because most infections at the ICU are device associated, we have chosen to present results of device-associated infections only.

Here we report the rates of VAP, CR-BSI, urinary catheter a demeure (CAD) associated urinary tract infection (CA-UTI), mortality and the effects of various risk factors. We also investigate the effect that the duration of the use of invasive devices has.

Material and methods

PREZIES, established in 1996, is a cooperation of participating hospitals, the Dutch Institute for Healthcare Improvement (CBO), and the National Institute for Public Health and the Environment (RIVM). During the period July 1997–December 2000 19 Dutch hospitals (c. 20% of all hospitals in The Netherlands) with 23 ICUs prospectively collected data on intensive care patients on a daily basis according to the PREZIES protocol. Both university and other hospitals participated, but university hospitals were relatively better represented (three out of seven). The study period varied between 2 and 39 months, with a median of 14. The average capacity of the participating ICUs was 8 beds (range 5–12).

Experts in the field of intensive care medicine and nosocomial infections developed the protocol in consultation with the participating hospitals. In each hospital a multidisciplinary team of the infection control professional, ICU nurses, the medical microbiologist, and the ICU physician performed the surveillance. The procedure of data collection and the tasks of the involved persons were established within each hospital. The definitions of pneumonia, sepsis, UTI, and risk factors were standardized and based on those of the CDC/NNIS system. An infection was deemed device associated when the day of or the day before the infection occurred was a device day.

All patients who stayed at the ICU for 48 h or more were included in the surveillance and followed from admission until discharge, death, or the day of withholding treatment because of their moribund condition. The study period per patient was restricted up to 56 days. After discharge from the ICU patients were followed-up for infection for another 24 h. The surveillance included 4,105 patients, for 3,921 of whom sufficient data were available. Of these patients 1,277 (33%) had an infection when entering the ICU and were analyzed separately (data not shown). The remaining 2,644 patients remained at the ICU for a total of 25,432 days. Median ICU stay was 6 days, interquartile range (IQR) 6 days. Patient characteristics of patients with and without a device-associated infection are presented in the Electronic Supplementary Material (ESM; Appendix A).

The following patient characteristics were recorded: demographic data, medical discipline treating the patient (specialty), Acute Physiology and Chronic Health Evaluation (APACHE) II score, immunity status (normal immunity, leukopenia (leukocytes polymorphonuclear cells $< 0.5 \times 10^9$/l), and otherwise impaired immunity (defined as a chronic low or recent high dose of corticosteroids, chemotherapy, dialysis or systemic diseases such as leukemia or AIDS in patients with leukocytes polymorphonucelair cells $> 0.5 \times 10^9$/l), origin (e.g., community, ward) and whether admission was acute or elective. The use of medical devices (mechanical ventilation (including intubation without ventilation and/or having a tracheostoma); CVC and indwelling transurethral or suprapubic catheter), systemic antibiotics, and selective decontamination of the digestive tract (SDD) were recorded daily. Two or more CVCs on 1 day were counted as one CVC day. For each nosocomial infection the infection date, type of infection, and microbiological test result were recorded. Pneumonias recorded within 4 days from an earlier pneumonia in the same patient, and sepsis and UTI occurring within 7 days after the same kind of infection were not regarded as new infections, according to the European protocol for nosocomial infection surveillance [6]. This led to the exclusion of about 2.5% of infections but did not affect the calculation of risk factors, as only the first VAP, CR-BSI, or CA-UTI was included in the regression analysis. Any new pathogens with these excluded infections were presented with the former infection. In patients who developed a device-related infection the time at risk was defined as the number of days from the first day on which the device was used until the day on which the device-related infection was diagnosed or, if no infection occurred, until the last day of device use. Observations were censored if the device was no longer used or if the patients with the device were transferred to other hospitals, deceased, or when active (life-supporting) treatment was withheld. Before aggregation individual

data were checked for completeness and consistency. Patient and treatment characteristics were determined in patients with and without infection. The incidence of infections per 1,000 device days was calculated. To calculate the incidence density of subsequent periods the numbers of days at risk of a patient were divided over and thus contributed to the subsequent categories, as described by McLaws and Berry [7].

Kaplan-Meier survival analysis and Cox regression in SAS version 9.1 (SAS Institute, Cary, N.C., USA) were used to calculate the relative risk of acquiring infection for patient and treatment characteristics with regard to the time at risk. Logistic regression was used to determine the effect of duration of device use on infection and the effect of risk factors on mortality. For uniformity we used the same categories of risk factors for all infections. Risk factors with a p value of 0.20 or less in the univariate regression were initially included in the multiple regression models. The model was reduced by means of manual backward elimination. Risk factors contributing significantly to the goodness of fit of the model but not statistically significant independent risk factors in themselves are also shown. Statistical significance was defined at $p \leq 0.05$.

Results

Device-related infection rates, and ICU stay

Overall 58% of patients were mechanically ventilated (568 days per 1,000 ICU days), 61% had a CVC (506 days per 1,000 ICU days), and 86% had an indwelling catheter (818 days per 1,000 ICU days). As many as 71% had two or more different devices during (part of) their ICU stay and 43% had all three.

Of all pneumonia cases 86% were associated with mechanical ventilation. VAP occurred in 19% of ventilated patients, with an incidence of 25 per 1,000 ventilator days. Of all sepsis cases 34% were related to a central vascular catheter. Of the patients with a CVC 3% developed CR-BSI, with an incidence of 4 per 1,000 CVC days. Of all UTI cases 95% were associated with the use of an indwelling catheter. CA-UTI occurred in 8% of the patients with an indwelling urinary catheter, with an incidence of 9 per 1,000 CAD days. Median ICU stay was 7 days (IQR 7) in ventilated patients without VAP and 17 days (IQR 17) in those with infection; 6 days (IQR 8) in patients with a central vascular catheter without CR-BSI and 24 days in those with infection; and 6 days (IQR 6) in patients with a urinary catheter without CA-UTI and 18.5 days (IQR 16.5) in those who developed infection. Table 1 shows the median duration of device use and the IQR. Patients who developed a device-associated infection had significantly longer ICU stays.

Duration of device use as a risk factor for infection

Figure 1 shows the incidence densities of patients at risk that developed an infection, according to the duration of mechanical ventilation, central vascular catheterization, or urinary catheterization. The incidence density of CR-BSI and CA-UTI varied relatively little according to duration of CVC and CAD use, but that of VAP decreased when the ventilation lasted longer than 9 days. We also calculated the VAP risk per day. Fig. 2 presents the risk of patients expressed as a proportion of those at risk for at least the number of indicated days. The risk increased until day 5, remained more or less constant until day 10 and decreased thereafter.

There were too few patients at risk for more than 3 weeks to draw conclusions. Therefore we summarize these. Cox regression takes into account the effect of time at risk, but its relative risks do not provide insight into its effect. Logistic regression does not integrate the time at risk in the calculation of its odds ratios. However, this makes it possible to express the effects of discerned periods at risk. Therefore Table 2 shows the odds ratios of increased device use (until infection), determined by univariate logistic regression. Prolonged device use significantly increased the risk of acquiring a device-associated infection. The risk of CR-BSI was affected most: the

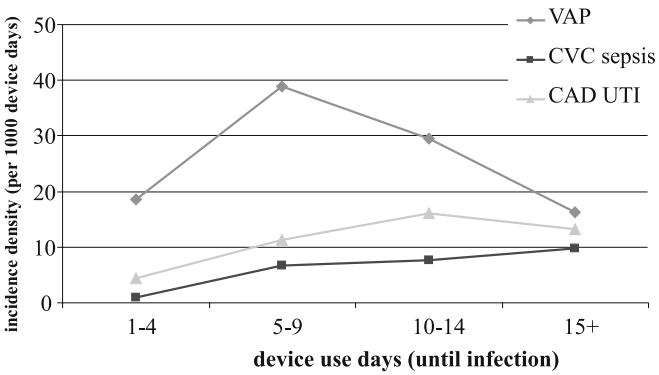

Fig. 1 Incidence density of device-associated infections per 1,000 device days, according to duration of device use

Table 1 Median duration of device use in all patients, those who develop device-associated infection (*DAI*) and until infection (*parentheses* IQR)

	All patients on device	All patients with DAI	Until first DAI
Ventilation	6 (9)	14 (15)	6 (5)
Central venous catheterization	5 (5)	21 (16)	9 (13)
Urinary catheterization	6 (7)	17 (17.5)	8 (9)

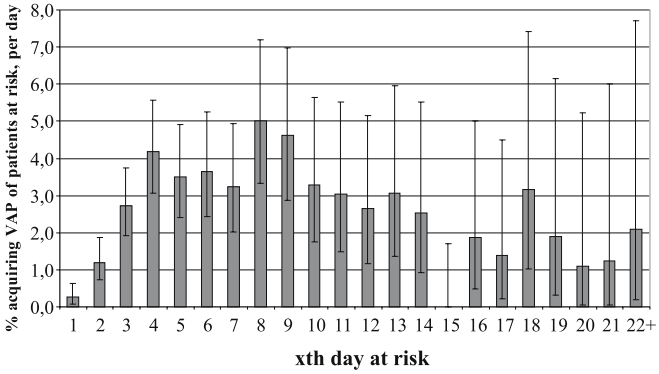

Fig. 2 The proportion of all patients ventilated for X days or longer that develop VAP at day X and 95% confidence intervals

odds ratio for a CVC in situ for 5–9 days was 4.3 and for a period of 10 days or longer 8.4. Device use affected the risk of VAP the least. Being on a ventilator for at least 10 days was not associated with a higher risk than being ventilated for 5–9 days. This is reflected in the decreasing incidence density in Fig. 1.

Other risk factors for infection

Incidence densities for different categories of patients are presented in the ESM (Appendix B). Table 3 presents the relative risks determined by multivariate Cox regression (univariate results in the ESM, Appendix C). Female sex and SDD use were associated with lower VAP risk. An APACHE II score of 20 or greater was associated with a higher risk. Only SDD use affected the VAP risk significantly. The only independent risk factor for CR-BSI was acute admission. Acutely admitted patients had a lower risk for CR-BSI. Independent risk factors for CA-UTI were female sex, impaired immunity, acute admission, and systemic antibiotics. Acute admission had no proportional hazard over time, indicating that the effect of this risk factor changed over time. To account for this an interaction term with time at risk was included in the analysis. The effect of acute admission was highest at the start of the urinary catheterization and decreased with continuing ICU stay/catheterization at a factor of 10% per day.

Table 2 Odds ratios for duration of device use, determined by univariate logistic regression (*parentheses* 95% confidence intervals)

	Duration of device use		
	1–4 days	5–9 days	≥ 10 days
Ventilation	1	1.9* (1.4–2.6)	1.6* (1.1–2.2)
Central venous catheterization	1	4.3* (1.7–10.7)	8.4* (3.4–20.4)
Urinary catheterization	1	1.6* (1.0–2.4)	3.3* (2.2–4.9)

* $p < 0.05$

Table 3 Relative risks for infection (*parentheses* 95% confidence intervals), based on multivariate Cox regression. Analysis of risk factors for which interaction with time was significant was executed with interaction terms included for all categories; however, only significant interactions are shown (*VAP* ventilator-associated pneumonia, *CR-BSI* central venous catheter related bloodstream infection, *CA-UTI* catheter-associated urinary tract infection, *APACHE* Acute Physiology and Chronic Health Evaluation, *SAB* systemic antibiotics)

	VAP	CR-BSI	CA-UTI
Sex			
Male	1	–	1
Female	0.8* (0.6–1.0)	–	1.4* (1.0–1.8)
APACHE II			
0–19	1	–	–
≥ 20	1.2 (1.0–1.5)	–	–
Immunity			
Not impaired	–	–	1
Leukopenia	–	–	–[a]
Otherwise impaired immunity	–	–	2.5** (1.5–4.0)
Admission			
Planned	–	1	1
Acute	–	0.5** (0.3–1.0)	1.8* (1.0–3.3)
Interaction with time			0.9** (0.9–1.0)
SDD			
No	1	–	–
Yes	0.6** (0.4–0.9)	–	–
SAB at admission			
No	–	–	1
Yes	–	–	0.5** (0.3–1.0)

* $0.05 < p < 0.1$
** $p < 0.05$
[a] No cases in category

Table 4 Odds ratios for mortality (*parentheses* 95% confidence intervals), based on multivariate logistic regression (*MV* mechanical ventilation, *CVC* central venous catheter, *UT* urinary catheter, *SAB* systemic antibiotics)

	MV ($n=1,516$)	CVC ($n=1,604$)	UT ($n=2,259$)
Age			
≤ 39 years	1	1	1
40–70 years	1.7** (1.1–2.8)	1.3 (0.8–2.2)	1.6** (1.0–2.5)
≥ 70 years	3.0** (1.9–4.8)	2.7** (1.6–4.5)	2.8** (1.8–4.4)
APACHE II			
0–19	1	1	1
≥ 20	1.9** (1.5–2.4)	1.7** (1.3–2.3)	1.9** (1.5–2.4)
Specialty			
Surgery, traumatology	1	1	1
Internal medicine	1.7** (1.5–2.7)	2.1** (1.5–2.9)	1.9** (1.4–2.7)
Cardiology/cardiosurgery	2.4** (1.6–3.6)	2.4** (1.6–3.6)	2.6** (1.8–3.8)
Neurology/neurosurgery	1.8** (1.2–2.8)	1.9** (1.2–3.2)	1.8** (1.2–2.7)
Other	1.3 (0.8–2.1)	1.8** (1.1–2.8)	1.4 (0.9–2.2)
Admission			
Planned	–	–	1
Acute	–	–	1.4** (1.0–1.8)
SAB at admission			
No	1	1	1
Yes	1.6** (1.1–2.4)	1.4 (0.9–2.1)	1.5** (1.1–2.3)
Ventilation			
No	–	1	1
Yes	–	3.9** (2.5–6.0)	4.8** (3.3–7.0)
CVC			
No	1	–	1
Yes	1.7** (1.2–2.3)	–	1.8** (1.3–2.5)
Duration of device use			
< 4 days	1	1	–
5–14 days	1.5** (1.1–2.0)	1.6** (2.0–4.0)	–
> 15 days	1.6** (1.1–2.2)	2.8** (2.5–6.0)	–

* $0.05 < p < 0.1$
** $p < 0.05$

Mortality

Developing VAP was not associated with a higher crude mortality (26.0% and 23.2% in patients with and without infection, respectively). Developing a CR-BSI or a CA-UTI was associated with a (nearly) significantly higher crude mortality: 30.9% vs. 20.2% ($p = 0.06$) in patients with a CVC and 26.7% vs. 16.7% ($p = 0.002$) in patients with a CAD. In multivariate regression developing a device-associated infection was not associated with mortality (Table 4).

Micro-organisms

Only the culture of the first infection of its kind is given here. During the first 4 days of ventilation 37% of the isolates for VAP were flora associated with early-onset VAP: *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Haemophilus influenzae*. In pneumonia patients ventilated for 5 days or more less *H. influenzae* was isolated and more *Pseudomonas aeruginosa* and Enterobacteriaceae. In CA-UTI patients intestinal flora contributed 69% in the first 4 days. This decreased to 44%, whereas *P. aeruginosa* and *Klebsiella pneumoniae* increased in frequency. Staphylococci were found in 60% of the isolates of CR-BSI patients in the first 2 weeks. After 2 weeks they were only found in 41% of the isolates whereas Enterobacteriaceae were more frequently found with increasing duration of CVC.

Discussion

This is one of the few prospective studies to investigate both the incidence of and the risk factors for different types of device-related ICU-acquired infections as well as their effect on mortality in the same patient population. Nearly every fifth ventilated patient without a preexisting infection admitted for 48 h or more at Dutch ICU's developed VAP. Infection rates in patients with a CVC or CAD were 3% and 8% respectively. Longer device use increased the risk of acquiring an infection, especially CR-BSI, and CA-UTI. Device-associated infections did not significantly increase the mortality of device-assisted patients after adjustment for case-mix.

Device utilization rates and infection rates

Device use was high in our population. The overall mean ventilator use rate reported by the NNIS was approxi-

mately 40% [8] whereas this was 58% in our study. The same applies for central line use (approx. 50% and 61%, respectively) and urinary catheter use (70% and 86%, respectively). These differences could be the result of different selections of patient populations (all ICU patients in NNIS vs. patients staying at least 48 h in this study) which is likely to be reflected in their need of device assistance, but also of differences in patient management. The inclusion criterion of ICU stay 48 h or longer in our study probably resulted in higher infection incidence rates. Also, some publications report incidence density rates calculated with all ICU or device days instead of the number of days up to infection, resulting in lower rates, as pointed out for ventilated patients by Eggimann et al. [9]. This is the case with figures derived from NNIS data [8].

Our pneumonia rate of 19% in ventilated patients and 25 per 1,000 ventilator days falls within the reported rates in more recent studies with comparable methods of diagnosing VAP (cultures usually from endotracheal aspirates or sputum): 9.8/1,000 ventilator days [8], 15% [10], 15% [11], and 44.0 per 1,000 ventilator days at risk [9], although it seems relatively high. In our study a pneumonia was considered VAP when the infection day or the day before was a ventilator day. Many studies consider VAP when a patient is ventilated longer than 48 h [12]. This difference may account in part for a relatively high VAP rate. The CR-BSI rate among patients with a central line was 3%. This figure is comparable to rates in other studies [13, 14, 15]. Our CA-UTI rate of 8% was also in accordance with earlier reported CA-UTI rates [16, 17, 18].

Risk factors for infection

The increased VAP, CR-BSI, and CA-UTI risk as a consequence of device use (in general) and the effects of some of the other risk factors, for example, sex, were comparable to those reported previously [11, 19, 20]. After much debate [21, 22, 23] a recent Cochrane review concluded that SDD, aimed at eradicating colonization of aerobic, potentially pathogenic micro-organisms from the oropharynx, stomach, and gut, does benefit the ventilated patient [24]. In accordance with this, we found a decreased relative risk of acquiring VAP when receiving SDD. Although reported in several other studies, the use of systemic antibiotics was not associated with VAP in this group. Ibrahim et al. [11] found that multiple central venous line insertions increased the VAP risk, but in our data a central vascular catheter was not associated with a higher VAP risk. Also, in CVC patients, ventilation did not affect the risk of CR-BSI, unlike the findings in another study [19]. An unexpected and unaccountable finding was acute admission lowering the risk of CR-BSI. Impaired immunity increased the CA-UTI risk whereas the use of systemic antibiotics at admission was associated with a lower risk. Ventilation or a central vascular catheter did not affect the CA-UTI risk in our study.

Duration of device use

Our data showed that a longer time at risk increases the chance of infection. However, this association was less for VAP, when ventilation lasted longer than approx. 10 days, indicating that ventilation provokes pneumonia relatively early, rendering patients remaining ventilated without infection as "survivors" with lower intrinsic risk for VAP [25]. The incidence density was highest in patients ventilated for 5–9 days (Fig. 1). Figure 2 shows that the proportion of patients developing VAP increased until day 5. Thereafter the proportion remained more or less constant until day 10 and declined slightly thereafter, although this was not statistically significant. An increase in VAP risk during the first 5 days or so, as we observed, has been reported by almost all studies [25, 26, 27]. The results in patients ventilated for a longer period are less consistent. Unfortunately, the different ways of expressing the daily risk complicates comparisons between studies.

Duration of CVC use was a major risk factor for CR-BSI (odds ratio 5–9 days 4.3, and $\geq$ 10 days 8.4, vs. 1–4 days). This is consistent with the results of other studies; a duration of a central vascular catheter longer than 7 days was associated with an up to 8.7 times increased risk for CR-BSI [19]. Duration of urinary catheterization of 5 days or longer was a risk factor for urinary tract infection, which is in accordance with other findings [20]. These risk factors are of importance when stratifying nosocomial infection risks for interhospital comparison. Furthermore, some of them can be modified as to lower the infection risk. Several studies have reported that the duration of ventilation was successfully reduced without adverse patient outcomes [28, 29, 30]. Although less complex to achieve and perhaps therefore not a subject of explicit study, the timely removal of central vascular catheters and urinary catheters is of great importance because reducing the device duration can also reduce these patients' risk of developing an infection [31].

Mortality

Nosocomial pneumonia is associated with a high crude mortality, ranging from 20% to 71% [12]. We found that VAP is associated with a relatively low crude mortality of 26%, not significantly different from that in ventilated patients without VAP. Crude mortality was significantly higher in patients with CR-BSI and CA-UTI. However, neither VAP, CR-BSI, nor CA-UTI was associated with mortality when adjusted for other risk factors. Some studies have found VAP to be an independent risk factor for mortality while others have not [11, 32, 33, 34]. Some authors conclude this to be related to the used diagnostics. In recent studies CR-BSI is not associated with a significant attributable mortality. Case-control studies have found

similar crude as well as adjusted mortality rates in patients with and without CR-BSI [35, 36, 37].

Laupland et al. [17] studied ICU-acquired UTI in a large cohort of ICU patients over 90% of whom had a urinary catheter and also found a comparable difference in crude mortality between patients with and without UTI. An ICU-acquired UTI was, however, not an independent risk factor for death. In CA-UTI this may be due to the fact that UTI can simply be a marker of other serious conditions [20]. There are very few other studies which include both nosocomial infection and duration of device use as risk factors for mortality. Increased duration of device use was an independent risk factor for mortality with ventilated patients and patients with a central line, but not in patients with a urinary catheter. In patients on a ventilator or with a CVC the duration of device use is related to the development of the patient's condition in the ICU and therefore closely associated with mortality. Being in need for both ventilation and a CVC increased the mortality risk, compared with needing ventilation or a CVC only. For ventilation this association was stronger than that with APACHE II score determined within the first 24 h. When all patients, both device-assisted and not, were considered, developing nosocomial sepsis or two or more nosocomial infections independently increased mortality (data not shown).

Pros and cons of this surveillance based study

The patient-based surveillance of ICU-acquired infections in 19 hospitals, taking into account duration of device use, resulted in an extensive, detailed database. Surveillance using a standard protocol with standardized infection definitions for prospective surveillance on a daily basis has been shown to present the greatest sensitivity and specificity for the identification of nosocomial infections [38]. A drawback of observational studies is that not all confounding variables can be taken into account. Furthermore, we included the use of all three devices in our analyses, but we did not adjust for the occurrence of a possible earlier infection of another type. Data on antibiotic resistance of the cultured micro-organisms were not collected. However, mean resistance levels in Dutch hospitals and ICUs are known to be low [39].

Conclusions

Duration of device use was an important risk factor for VAP, CR-BSI, and CA-UTI. The risk for VAP increased until day 5 and remained fairly constant until day 10. Device-associated infections were not independently associated with mortality, but (duration of) ventilation and (duration of) CVC use were. When investigating which patient groups in an institution would benefit most from infection prevention strategies, factors such as device use, time at risk, APACHE II score, intravenous antibiotics at admission, immunity, sex, and acute admission must be considered. These risk factors are also of importance when stratifying for device-associated infection risks for interhospital comparison. The protocol that we used was designed for comparing the incidence of different types of ICU-acquired infections and therefore included a broad range of risk factors. The surveillance results formed a good basis to develop more specified protocols. Now Dutch hospitals can use specific surveillance protocols for CR-BSI and VAP which take more treatment specific risk factors into account and may better support infection prevention policy on the ICU.

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