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Nosocomial Infections in Critically Ill Infectious Disease Patients: Results of a 7-Year Focal Surveillance

Summary: An incidence study on nosocomial infections in critically ill infectious disease patients was carried out in the intensive care unit (ICU) of a university hospital for infectious diseases over a 7-year period (1 January 1990 to 31 December 1996). A total of 660 patients who stayed in the ICU for over 48 h were prospectively observed. The patients were divided into two groups: one with central nervous system infections (442 patients) and the other with other severe infections (218 patients). The risk of nosocomial sepsis and pneumonia was significantly higher in patients suffering from severe central nervous system infections. The incidence of sepsis was 24.2% vs 11.4% (relative risk 1.95; 95% confidence interval 1.32–2.89); the incidence of pneumonia was 30.5% vs 14.7% (relative risk 2.09; 95% confidence interval 1.47–2.96). The incidence of urinary tract infection was 14.3% vs 13.3% (relative risk 1.07; 95% confidence interval 0.71–1.61). Density rates of nosocomial septic episodes were 21.1±37.1 vs 11.7±32.4 episodes/100 central venous-line days (P<0.006). Nosocomial pneumonia occurred only in mechanically ventilated patients (36.9±61.2 vs 28.5±65.8 episodes per 1000 ventilatory days, P=0.012). Nosocomial urinary tract infection occurred only in patients with urinary catheters (11.6±60.7 episodes/1000 urinary catheter days vs 18.7±90.1, P=0.886). Multivariate regression analysis identified age, diagnosis of CNS infection, duration of urinary tract catheterization, the use of central venous lines and mechanical ventilation as independent risk factors of nosocomial sepsis. Duration of mechanical ventilation, use of steroids and diagnosis of CNS infection were independent risk factors of nosocomial pneumonia. A subanalysis identified tetanus patients to be at particular risk of nosocomial infections.

Introduction

Nosocomial infections are still one of the greatest problems of modern intensive care medicine because of the frequent use of invasive procedures and drugs such as antibiotics, H_2-blockers or steroids which increase the risk of infection [1–4]. Nosocomial infections are associated with higher intensive care unit (ICU) mortality, longer stay in intensive care and higher cost of treatment [5–7].

The results of the nosocomial infection surveillance in various types of ICU's are often presented together. Seldom are groups of ICU patients selected based on a separately evaluated admission diagnosis. Therefore, the risk and incidence of nosocomial infections in selected groups of ICU patients are often unrecognized, and instead are included in the total results of surveillance.

The aim of this study was to evaluate the incidence of nosocomial infections and risk factors for their acquisition in patients admitted to the ICU because of severe infections. Since nosocomial sepsis, pneumonia and urinary tract infections are the most common in all types of ICU patients, we focused only on these infections. We supposed that patients with central nervous system (CNS) infections were at increased risk because of prolonged consciousness disturbances and suppression of physiologic functions resulting in prolonged use of invasive procedures [8]. Therefore, patients with CNS infections (CNS-infections group) were evaluated separately and then compared to patients suffering from non-CNS severe infections.

Methods

During the study period (1 January 1990 to 31 December 1996), all critically ill adult patients with infectious diseases (ID) admitted to the six-bed intensive care unit of a teaching hospital and hospitalized for more than 48 h were included in the study and prospectively followed for the occurrence of new episodes of nosocomial sepsis, pneumonia and urinary tract infection (UTI) acquired in the ICU. Patients with infections who required admission to the ICU because of the need for intensive monitoring and therapy included those with community and hospital infections acquired in other hospitals but who transferred to our ICU for further treatment.

Patient data was collected at the bedside and entered directly onto a computer using a custom-designed program (Access). Diagnosis of new nosocomial infections acquired in the ICU was documented according to the standard definitions of the Centers for Disease Control and Prevention (CDC) [9]. The number of pa-

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Table 1: Characteristics of the 660 critically ill infectious disease patients hospitalized in the intensive care unit (ICU) for more than 48 hours on admission, and ICU outcome (1990–1996).

	Reasons for admission to the ICU		P value
	CNS infections (442 patients)	Other infections (218 patients)	
Age (mean ± SD, years)	47.5 ± 20.1	53.5 ± 21.9	0.0002
Sex			
Male (no. pts. %)	262 (59.3)	145 (66.5)	0.09
Hospitalization before ICU admission (no. pts. %)	293 (66.3)	107 (49.1)	< 0.0001
Duration of hospitalization before ICU admission	5.9 ± 11.2	20.9 ± 99.4	0.19
APACHE II on the first ICU day	15 ± 9	19 ± 9	0.00004
Glasgow Coma Score	11 ± 4	12 ± 4	0.04
median	13	14	
< 15, no. pts. (%)	294 (66.5%)	133 (61%)	0.19
Duration of ICU hospitalization (mean ± SD, days)	20.3 ± 20.6	14.1 ± 14.6	0.00002
ICU mortality	168 (38%)	55 (25.0)	0.0015

CNS = central nervous system; SD = standard deviation; no. pts. = number of patients.

tients with nosocomial sepsis or the number of episodes of nosocomial sepsis did not include patients or episodes of nosocomial pneumonia or UTI with positive blood cultures. These patients were included in the number of patients who acquired nosocomial pneumonia or UTI. The data on nosocomial infections were also put in the same database. The data were collected prospectively by two authors (*B. B.* and *I. K.*).

Two groups of patients were evaluated separately. In the first group were patients admitted to the ICU because of central nervous system infections (CNS infection group). In the second were patients admitted because of other, non-CNS infections (non-CNS infection group). Diagnosis of CNS infection was based on symptoms and signs of the illness and the examination of the cerebrospinal fluid. Diagnosis of these and other infections that required ICU treatment was based on clinical and laboratory criteria, including bacteriologic and serologic tests. Patients with bloodstream infection and consequent CNS affection were included in the CNS infection group of patients.

The following variables were recorded to analyze the predisposing factors for developing nosocomial infection: age, sex, reason for admission to the ICU, APACHE II and Glasgow Coma Score on the first ICU day, hospitalization before ICU admission, duration of hospitalization in the ICU, device utilization (mechanical ventilation, central venous lines, nasogastric intubation, urinary catheter, use of steroids and H_2 blockers (cimetidine or ranitidine). Device days consisted of the number of ventilator days, number of central line days, nasogastric tube days and urinary catheter days [10, 11]. The ventilator circuits were changed at an interval longer than 1 week. Selective digestive tract decontamination was not used. Gastric enteral feeding was used in all patients with inserted nasogastric tubes and without disturbances of gastric emptying.

The results are expressed as mean with standard deviation for continuous variables or frequencies for categorical data. The characteristics between the two groups of critically ill infectious disease patients were compared using the Mann-Whitney U test for continuous variables. For dichotomous variables the chi-square test and relative risk, their limits, and their 95% confidence levels of significance were calculated using standard methods. The level of significance was defined as $P<0.05$. All univariate associations with $P<0.05$ were tested using multivariate logistic regression (forward step) to identify variables independently associated with nosocomial sepsis, pneumonia and urinary tract infections. The statistical analysis was performed on a computer with Statistica software (StatSoft, Tulsa, OK, USA).

Results

Between 1990 and 1996, a total of 660 critically ill infectious diseases patients were hospitalized in our ICU for more than 48 h. Four hundred forty-two (67%) of them were admitted because of central nervous system infections and 218 (33%) because of non-CNS infections. Table 1 illustrates demographic characteristics, length of ICU stay and ICU outcome for both groups. Patients in the non-CNS infection group were older.

Patients with CNS infections were more frequently hospitalized in other hospitals or wards before ICU admission. Their average length of stay in the ICU was for about 6 days longer than that of patients with non-CNS infections ($P=0.00002$, Mann-Whitney test). ICU mortality was also significantly higher. APACHE II and Glasgow Coma Score were significantly higher in the non-CNS infection group.

Table 2 presents admission diagnoses for both groups and etiologic agents of the most common infections that were the reason for admission to the ICU. Thirty-one patients (7%) in the CNS-infection group had one or more noso-

Table 2: Infections that caused admission to the ICU and their etiologic agents.

CNS infections (442 patients)	
Bacterial CNS infections: (n = 193; 176 community acquired; 17 nosocomial)	
Bacterial meningitis	n = 160 (100%)
Streptococcus pneumoniae	71 (44.4%)
Neisseria meningitidis	14 (8.8%)
Staphylococcus aureus	7 (4.4%)
Streptococcus pyogenes	5 (3.1%)
Acinetobacter baumannii	5 (3.1%)
Listeria monocytogens	5 (3.1%)
Pseudomonas aeruginosa	4 (2.5%)
Escherichia coli	3 (1.9%)
Haemophilus influenzae	3 (1.9%)
Streptococcus viridans	3 (1.9%)
Other	5 (3.1%)
Unknown	35 (21.9%)
Intracranial abscess	n = 33 (100%)
Fusobacterium nucleatum	1 (3%)
Streptococcus milleri	1 (3%)
Staphylococcus aureus	1 (3%)
Unknown	30 (91%)
Viral and postviral encephalitis	n = 114 (100%)
Tick-borne encephalitis	19 (16.7%)
Herpes simplex virus	9 (7.9%)
Varicella-zoster virus	3 (2.6%)
Rabies	1 (0.9%)
Coxackie virus	1 (0.9%)
Unknown	81 (71%)
Tuberculous meningitis	19
Myelitis, Guillain-Baré syndrome, polyneuritis	30
Cryptococcal meningitis	4
Cysticerosis	2
Tetanus	78
Botulism	2

Other non-CNS infections (218 patients)	
Sepsis (n = 111; 96 community acquired; 15 hospital acquired – 100%)	
Staphylococcus aureus	25 (22.5%)
Escherichia coli	17 (15.3%)
Klepsiella pneumoniae	6 (5.4%)
Proteus mirabilis	5 (4.5%)
Pseudomonas aeruginosa	5 (4.5%)
Candida spp.	5 (4.5%)
Staphylococcus epidermidis	4 (3.6%)
Acinetobacter baumannii	3 (2.7%)
Streptococcus pyogenes	3 (2.7%)
Enterococcus spp.	3 (2.7%)
Other bacteria	8 (7.2%)
Unknown	31 (27.9%)
Pneumonia (n = 64; 58 community acquired; 2 hospital acquired – 100%)	
Legionella spp.	5 (8.3%)
Streptococcus pneumoniae	3 (5%)
Staphylococcus aureus	3 (5%)
Other	4 (6.7%)
Unknown	45 (75%)
Generalized viral infections with organ failures	n = 14 (100%)
Hantaan virus	7 (50%)
Echo virus	1 (7.1%)
Unknown	6 (42.9%)
Leptospirosis	9
Soft-tissue infections (n = 13; 11 community acquired, 2 hospital acquired – 100%)	
Streptococcus pyogenes	7 (53.8%)
Staphylococcus aureus	1 (7.7%)
Unknown	5 (38.5%)
Hepatitis with liver failure	3
Gastrointestinal infections, hypovolemic shock	4
Other infections	4

comial infections acquired in other hospitals/wards and in the group of patients with other-than-CNS infections 19 (8.7%) patients had such infections. These infections were not included among infections acquired in the ICU listed in Table 4.

Table 3 compares the incidence and the average device utilization days of the most common risk factors for the acquisition of nosocomial infections between the two groups. Invasive procedures such as mechanical ventilation, urinary catheters and nasogastric tubes were used significantly more frequently in patients with CNS infections than in other critically ill ID patients. The number of device days was significantly higher, as was the use of steroids and H_2-antagonists in patients with CNS infections. Central venous lines were inserted with the same frequency in both groups but were used for a longer period of time in the group of patients with CNS infections.

During the 7-year study period, nosocomial sepsis occurred in 134 (20.3%) patients (a total of 173 episodes); nosocomial pneumonia in 167 (25.3%) patients (a total of 270 episodes), and urinary tract infection in 92 (13.9%) of the critically ill infectious disease patients (127 episodes). Table 4 shows the etiologic agents of nosocomial infections. *Pseudomonas aeruginosa*, *Acinetobacter* spp. and *Klebsiella pneumoniae* are still the most common pathogens with high antibacterial resistance. Details on antibiotic sensitivity are presented elsewhere [12]. The risk of nosocomial sepsis and pneumonia was about two times higher in patients treated in the ICU because of CNS infections than in patients with other infections (Table 5). The risk of nosocomial urinary tract infection was the same for both groups. The rate of nosocomial sepsis was 13.4±53.7 episodes per 1000 patient ICU days in the CNS infection group and 5.9±18.9 episodes per 1000 patient ICU days in the non-CNS infection group (P=0.015, Mann-Whitney test). Analysis of patients with central venous lines showed that the number of all septic episodes per 1000 catheter days was also significantly higher in the

Table 3: Main risk factors for the acquisition of nosocomial infections in critically ill infectious diseases patients (1990–1996).

	Reasons for admission to the ICU: Central nervous system infections (442 patients)	Non-CNS infections (218 patients)	P value
Mechanical ventilation			
Number of patients (%)	304 (68.8)	106 (48.6)	< 0.0001
Duration, days (mean ± SD)	17.5 ± 17	14.1 ± 17	0.0025
Central venous lines			
Number of patients (%)	320 (72.4)	151 (69.3)	0.4559
Duration, days (mean ± SD)	15.2 ± 12.6	11.7 ± 11.3	0.0001
Urinary catheter			
Number of patients (%)	391 (88.5)	177 (81.2)	0.0157
Duration, days (mean ± SD)	19.7 ± 20.1	14.8 ± 16.8	0.0005
Nasogastric tube			
Number of patients (%)	329 (74.4)	134 (61.5)	0.0009
Duration, days (mean ± SD)	18.1 ± 19.4	12.7 ± 15.3	0.002
Prescription of steroids			
Number of patients (%)	97 (21.9)	18 (8.2)	< 0.0001
Prescription of H_2-antagonists			
Number of patients (%)	269 (60.1)	114 (52.3)	0.0441

SD = standard deviation.

Table 4: Etiologic agents of nosocomial infections in a 7-year surveillance period (1990–1996).

Microorganisms	Nosocomial infections No. of isolates (%) Sepsis (n = 275)	Pneumonia (n = 262)	Urinary tract infections (n = 151)
Escherichia coli	2 (0.7)	7 (2.7)	5 (3.3)
Klebsiella pneumoniae	39 (14.2)	36 (13.7)	28 (18.5)
Citrobacter freundii	2 (0.7)	2 (0.8)	3 (2.0)
Serratia marcescens	8 (2.9)	2 (0.8)	1 (0.7)
Proteus mirabilis	1 (0.4)	6 (2.3)	4 (2.6)
Enterobacter spp.	12 (4.4)	7 (2.7)	9 (6.0)
Pseudomonas aeruginosa	41 (14.9)	85 (32.4)	37 (24.5)
Acinetobacter spp.	69 (25.1)	56 (21.4)	15 (9.9)
Other gram negative bacteria	6 (2.2)	5 (1.9)	2 (1.3)
Enterococcus sp.	32 (11.6)	5 (1.9)	20 (13.2)
Staphylococcus aureus	14 (5.1)	32 (12.2)	3 (2.0)
Other staphylococci	25 (9.1)	9 (3.4)	–
Candida spp.	20 (7.3)	5 (1.9)	24 (15.9)
Other gram-positive bacteria	3 (1.1)	5 (1.9)	–

CNS infection group (21.1±37.1 vs 11.7±32.4 septic episodes/1000 central venous line-days, P=0.006, Mann Whitney test). Nosocomial pneumonia occurred only in mechanically ventilated patients. The rate of infection was 36.9±61.2 episodes per 1000 ventilator days in patients with CNS, and 28.5±65.8 episodes per 1000 ventilator days in patients with non-CNS infections (P=0.0284, Mann-Whitney test). UTI occurred only in patients with urinary catheters. The rate of infection was 11.6±60.7 episodes per 1000 urinary catheter days in patients with CNS, and 18.7±90.1 per 1000 urinary catheter days in patients with non-CNS infections (P=0.886, Mann-Whitney test). Therefore, univariate analysis showed that CNS infection proved to be a significant risk factor for the acquisition of nosocomial sepsis and pneumonia after the adjustment for device utilization days.

Multiple forward step regression analysis confirmed this. Results are presented in Table 6. It showed that age, length of mechanical ventilation, duration of central venous catheter and urinary catheter use and diagnosis of CNS infection on admission were associated significantly with nosocomial sepsis. Use of steroids, diagnosis of CNS

Table 5: Nosocomial infections in critically ill infectious diseases patients (1990–1996).

	Reasons for admission to the ICU				
	Central nervous system infections (442 patients)	Non-CNS infections (218 patients)	P value	Relative risk	95% CI
Type of nosocomial infection	No. of patients (%)				
Sepsis	107 (24.2)	27 (11.4)	0.0006	1.95	1.32–2.89
Pneumonia	135 (30.5)	32 (14.7)	0.00001	2.09	1.47–2.96
Urinary tract infections	63 (14.3)	29 (13.3)	0.83	1.07	0.71–1.61

CI = confidence interval.

Table 6: Results of the multiple forward step regression analysis for the dependent variables nosocomial sepsis and pneumonia.

Nosocomial pneumonia		
Independent risk factors	Beta	P value
Duration of mechanical ventilation	0.352586	< 0.0001
Use of steroids	0.181607	< 0.0001
Diagnose of CNS infection at admission	0.089723	0.00412
Nosocomial sepsis		
Independent risk factors	Beta	P value
Duration of urinary catheterization	0.401987	< 0.0001
Diagnosis of CNS infection at admission	0.131708	< 0.0001
Duration of the use of central venous catheters	0.182267	0.00038
Age	0.089967	0.00241
Duration of mechanical ventilation	0.185818	0.00262

infection on admission and length of mechanical ventilation were independent risk factors of nosocomial pneumonia.

Since the group of patients with tetanus was fairly large, we analyzed this group separately. Tetanus patients were older than other CNS patients (67.5±12 vs 43.2±18 years, P<0.0001), stayed in the ICU for a longer period of time (31.6±19 vs 17.8±20 days, P<0.0001), were more frequently mechanically ventilated (92.3% vs 63.7%, P<0.0001) and the duration of use was longer (25±14.1 vs 15±17.3 days, P<0.0001). Duration of central venous catheter use was longer (21.7±13 vs 13.4±11.8 days, P<0.0001) as well as of urinary catheterization (20.2±13.9 vs 10.4±11.9 days, P<0.0001). Steroids were more commonly used in patients with other than tetanus CNS infections (23.6% vs 9%, P=0.015). Nosocomial infections were significantly more frequent in tetanus patients than in patients with other CNS infections. Nosocomial sepsis was reported in 57.7% of tetanus patients (57 episodes) and in 17% (79 episodes) of other than tetanus CNS patients (P<0.00001). Its rate was 26.9±34.7 vs 10.5±57 episodes per 1000 patient ICU days (P<0.0001) or 36.5±37.3 vs 16.8±35.9 episodes per 1000 central venous catheter days (P<0.0001). Nosocomial pneumonia was reported in 55.1% (73 episodes) of tetanus patients and in 26.6% (156 episodes) of other than tetanus CNS patients (P<0.0001). Its rate was 36.6±40.7 vs 37±66.4 episodes per 1000 ventilator days (P=0.16). Urinary tract infections were reported in 19.2% (32 episodes) of tetanus patients and in 11.3% (56 episodes) of other than tetanus CNS patients (P<0.00001). Their rates were 25.8±116.3 vs 8.2±35.9 episodes per 1000 urinary catheter days (P=0.026). Despite this, ICU mortality in tetanus patients was 16.7% vs 43% in patients with other CNS infections (P<0.0001).

Discussion

We adopted a comprehensive method of continuous, focal surveillance for all sites of nosocomial infections in the ICU since 1988 [12–14]. It is known that the distribution of each nosocomial infection rate differs according to the type of ICU [10]. Until now the rates and risk of nosocomial infections have not been selectively evaluated in critically ill ID patients. In this prospective, 7-year surveillance of the three most common nosocomial infections, sepsis, pneumonia and UTI occurred in 20.3%, 25.3% and 13.9% of patients, respectively. During the study, various new diagnostic criteria for some nosocomial infections appeared [15]. We used CDC criteria for the diagnosis of nosocomial infections to ensure the comparability of data between years and with other ICUs [16, 17]. New pathogens emerged as a cause of nosocomial infections such as methicillin-resistant *Staphylococcus aureus*, and more frequent isolation of *Candida* spp., but gram-negative isolates still remain the most frequent cause of the

most common nosocomial infections. We identified a subgroup of critically ill ID patients who are at particular risk of nosocomial infections. These are patients admitted to the ICU because of CNS infections, particularly patients with tetanus. Analysis of the risk factors showed that the use of invasive devices in critically ill ID patients is frequent, as well as the use of some drugs that might increase the risk for at least some nosocomial infections. Moreover, the use of invasive procedures in our patients is prolonged. Invasive devices were more frequently used with more patient device days in patients with CNS infections than in the non-CNS infection group. Again, this particularly pertains to patients with tetanus. Steroids and H_2 blockers were also used more often in the CNS infection group, although the use of steroids was significantly reduced over the period of the study. In 1990, they were used in 46% of patients and in 1995 in 10%. Their use was more common in patients with CNS infections since we use them in the treatment of brain edema in patients with bacterial meningitis, or as a therapy of postinfectious encephalitis. Since their use was usually short term, we did not consider their use as a significant factor that might significantly contribute to the incidence of nosocomial infections, but multivariate analysis identified them as independent risk factors of nosocomial pneumonia. H_2 antagonists are commonly prescribed in prophylaxis of stress ulcers that are common in unconscious patients on mechanical ventilation [18, 19]. Their use might increase the risk of nosocomial pneumonia [20], although the subject still remains controversial [21, 22]. Our results did not support the thesis on increased risk of nosocomial pneumonia in patients receiving these drugs. The prolonged use of mechanical ventilation, nasogastric tube and urinary catheter in patients with CNS infections is the result of the protracted disturbances of consciousness or sedation in tetanus patients and subsequent suppression of physiologic functions [23]. It is well known that these devices significantly increase the risk of various nosocomial infections, as supported by numerous investigations [23, 24]. *Cunnion* reported recently the greater incidence of nosocomial pneumonia in patients with a lower Glasgow Coma Scale Score [25]. Glasgow Coma Scale Score was significantly lower in the group of patients with CNS infections, although we expected a greater difference. The difference did not change even when tetanus patients were excluded from analysis. Nosocomial sepsis was a common nosocomial infection in both groups of patients. Since patients with secondary bacteremia/sepsis and pneumonia or UTI were not included in the number of patients with sepsis, almost all registered septic episodes represent primary bacteremia/sepsis episodes. The presence of central nervous lines is the most important risk factor for the development of nosocomial sepsis [26], although our study showed the greatest correlation with prolonged urinary catheterization. In our previous studies, the source for 45% of nosocomial sepsis episodes was central venous line contamination [27]. In 36% of episodes, the origin of septic episodes could not be elucidated. Nine and 11% of central venous catheter insertions were complicated by nosocomial sepsis in two observational periods [28]. Other authors reported almost the same proportion of primary bacteremia episodes [29]. Our data might suggest that in many patients with nosocomial sepsis the urinary tract was the portal of entry but UTI infection remained undiagnosed. Increased incidence of nosocomial pneumonia in patients with CNS infections compared with non-CNS infection patients of the CNS patients can be explained as device-related infections (mechanical ventilation). Regarding UTI, we reported only patients with bacteriuria associated with pyuria or a new episode of fever without other underlying reasons. This is probably the reason for the lower than expected incidence of urinary tract infections in our group of patients. The other reason might be frequent use of antibiotics in infectious disease patients, which delayed the onset of bacteriuria in catheterized patients. Our results suggest that nosocomial infections are common in critically ill infectious disease patients due to the greater use of invasive devices. The risk of nosocomial infections was significantly greater in patients suffering from CNS infections in whom invasive procedures were applied more frequently and for a prolonged period of time than in patients with non-CNS infections. Our results confirm that in addition to continuous epidemiological surveillance of nosocomial infections in all patients treated in intensive care units, patients with CNS infections require special attention for infection control intervention.

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