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Pneumonia associated with invasive and noninvasive ventilation: an analysis of the German nosocomial infection surveillance system database

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Abstract *Purpose:* Pneumonia associated with invasive mechanical ventilation (IMV) is one of the indicator infections of the German Nosocomial Infection Surveillance System. In 2005 surveillance was extended to include pneumonia associated with noninvasive ventilation (NIV). The aim of this study was to determine the utilization of IMV and NIV and the associated incidence densities (IDs) of pneumonia and to compare the characteristics of pneumonia cases and the spectrum of associated pathogens. *Methods:* We analyzed the pooled data of 400 intensive care units (ICUs) with respect to three categories of pneumonia: pneumonia associated with IMV and NIV and pneumonia not associated with ventilation. Pooled ventilation utilization rates and pneumonia IDs were calculated in total and stratified by hospital size, hospital type and ICU type. *Results:* Four hundred ICUs with 779,500 admitted patients, 1,068,472 IMV days and 101,569 NIV days reported 6,869 cases of pneumonia between 2005 and 2007. Of these, 5,811 cases were associated with IMV, 160 with NIV and 898 were not associated with ventilation. The mean pneumonia IDs were 1.58 and 5.44 cases per 1,000 ventilator days for NIV and IMV, respectively. Pneumonia cases associated with IMV were younger, had a longer ICU stay before onset of pneumonia and were more often associated with gram-negative bacteria than cases associated with NIV; however, there were no differences in the proportion of secondary sepsis and death. *Conclusions:* This surveillance study including pneumonia associated with IMV and NIV and pneumonia not associated with ventilation shows significant differences of pneumonia IDs, patient characteristics and the spectrum of associated pathogens.

Keywords Ventilator-associated pneumonia · Mechanical ventilation · Noninvasive ventilation · Intensive care units · Surveillance

Introduction

Ventilator-associated pneumonia (VAP) is a serious and common complication of intensive care unit (ICU) treatment and is associated with a longer ICU stay, higher morbidity and mortality, increased consumption of resources and additional hospital costs [1, 2]. VAP rates can be reduced through multiple interventions such as for instance education programmes and VAP prevention bundles as well as through surveillance [3–5]. VAP is included as one of the indicator infections in nosocomial infection surveillance systems [6, 7].

Noninvasive ventilation (NIV) is used for an increasing range of indications [8–14], has been associated with

lower rates of serious complications, especially of nosocomial pneumonia [15–19], and the success of NIV has been found to be associated with improved survival [20]. NIV has been described among other measures as a potential strategy to prevent VAP [21] and the recommendation to use NIV whenever possible has been incorporated in guidelines for VAP prevention [22, 23].

The ICU module of the German Nosocomial Infection Surveillance System (ICU-KISS) has collected data on pneumonia associated with invasive mechanical ventilation (IMV) in individual ICUs and provided national reference rates since 1997. In 2005, surveillance was extended to include pneumonia associated with noninvasive ventilation in addition to invasive mechanical ventilation. The aim of this study was to determine the utilization of invasive and noninvasive ventilation and the associated incidence densities (IDs) of pneumonia in 400 German ICUs participating in the ICU-KISS module between 2005 and 2007 and to compare characteristics of pneumonia cases associated with different types of ventilation and the spectrum of associated pathogens.

Methods

Detailed methods of ICU-KISS have been described previously [5, 7, 24, 25]. In short, ICU-KISS uses a unit-based approach and determines the number of patients, patient days and device days of individual ICUs as a denominator for the calculation of device-associated infection rates. Only in case of occurrence of nosocomial infections are patient-based data collected. Ventilator-associated pneumonia is one of the three indicator infections besides central venous catheter-associated bloodstream infection and urinary catheter-associated urinary tract infection used to evaluate infection control management in ICUs. Data are collected by infection control personnel in individual ICUs and is submitted via a web-based surveillance portal to the central database of the national reference centre. Participants can use the data analysis function of the surveillance portal at any time to compare local IDs of indicator infections with the national reference calculated from the pooled data of all participating ICUs.

To enable comparisons between ICUs, standardized definitions for devices and nosocomial infections are used. Invasive mechanical ventilation is defined as continuous ventilation via endotracheal tube or tracheostomy and noninvasive ventilation as positive pressure ventilation with different pressure levels via face mask or helmet performed intermittently or continuously for at least 6 h per day. The use of continuous positive airway pressure (CPAP) alone is not regarded as noninvasive ventilation.

Nosocomial pneumonia is diagnosed according to CDC definitions from a combination of clinical, laboratory and radiological criteria as "clinically defined pneumonia" or with additional microbiologic results on associated pathogens as "pneumonia with common bacterial or fungal pathogens" or "atypical pneumonia" [6]. There are additional pneumonia definitions for pneumonia in immunocompromised patients and for infants and children less than 12 years old.

Pneumonia is considered to be associated with NIV or IMV if ventilation has been performed for at least 6 h (NIV) or at least 12 h (IMV) during the 48-h period before onset of pneumonia. If NIV as well as IMV has been performed within 48 h of the onset of pneumonia, pneumonia is considered to be associated with IMV. Pneumonia is considered to be not associated with ventilation if neither IMV nor NIV has been performed within 48 h before the onset of pneumonia for the minimum period described above.

For each episode of nosocomial pneumonia the following data are collected: date of ICU admission and of onset of pneumonia, age and sex of the patient, up to four associated pathogens and the material from which pathogens were isolated (tracheal secretion, bronchoalveolar lavage/protected specimen brush, blood culture, other) and the occurrence of complications such as secondary sepsis and death during the ICU stay.

Pooled mean and median ventilation utilization rates per 100 patient days with 25 and 75% quantiles and mean and median incidence densities (IDs) of pneumonia with 25 and 75% quantiles per 1,000 ventilation days were calculated. The following pneumonia IDs were calculated: pneumonia per 1,000 patient days without ventilation for pneumonia not associated with ventilation, pneumonia associated with IMV per 1,000 IMV days and pneumonia associated with NIV per 1,000 NIV days. Differences between ventilation utilization and associated pneumonia IDs were tested by the Wilcoxon test for two categories and the Kruskal-Wallis test for more than two categories or the chi-square test. The significance level was $P < 0.05$. All analyses were performed with SPSS version 14.0.

Results

A total of 474 ICUs participated in ICU-KISS between 2005 and 2007. Of these, 400 (84.4%) performed NIV, and 74 (15.6%) did not document any NIV days during the 3-year observation period. ICUs performing NIV did not differ from ICUs that did not perform NIV with respect to hospital type (university hospital, academic hospital, other hospital), hospital size (<600 beds vs. ≥600 beds) and ICU type (medical, surgical, medical-surgical). Further analysis was based on data of the 400 ICUs performing IMV and NIV, and the characteristics of these ICUs are shown in Table 1.

Table 1 Characteristics of the 400 ICUs and the patient population included in this study

Parameter	Number (%)
No. of ICUs	400
Characteristics of ICUs	
Size of hospitals (no. of beds), median	456
No. of hospitals with <600 beds (%)	240 (60)
No. of hospitals with ≥600 beds (%)	160 (40)
Type of hospital	
No. of university hospital ICUs (%)	61 (15.3)
No. of teaching hospital ICUs (%)	189 (47.2)
No. of other hospital ICUs (%)	150 (37.5)
Size of ICU (no. of beds), median	10
Type of ICU	
No. of medical-surgical ICUs (%)	203 (50.7)
No. of medical ICUs (%)	71 (17.7)
No. of surgical ICUs (%)	69 (17.3)
No. of other ICUs (%)	57 (14.3)
Patient population	
No. of patients	779,500
No. of patient days (pd)	2,710,451
No. of ventilation days (IMV + NIV)	1,170,041
No. of invasive mechanical ventilation (IMV) days	1,068,472
No. of noninvasive ventilation (NIV) days	101,569

No number, *ICU* intensive care unit, *IMV* invasive mechanical ventilation, *NIV* noninvasive ventilation

Pooled mean ventilation utilization rates were 3.75 per 100 patient days for NIV and 39.42 per 100 patient days for IMV and pooled mean ventilator-associated pneumonia IDs were 1.58 and 5.44 cases per 1,000 ventilation days for NIV and IMV, respectively. The mean ID of pneumonia not associated with ventilation was lower with 0.58 cases per 1,000 patient days without ventilation.

For IMV but not for NIV there were significant differences in the utilization of ventilation between ICUs in small and large hospitals as well as between ICUs in university, teaching and other hospitals and ICUs of different types (Table 2). The hospital type and size did not influence pneumonia IDs associated with IMV, only the type of ICU affected pneumonia IDs with surgical ICUs having significantly higher median pneumonia IDs than other types of ICUs (Table 2). No significant differences of pneumonia IDs could be determined in any of the categories (hospital type and size, ICU type) for pneumonia not associated with ventilation and pneumonia associated with NIV.

A total of 6,869 cases of nosocomial pneumonia occurred during the analyzed 3-year period. Of these, 5,811 cases were associated with IMV, 160 were associated with NIV, and 898 were not associated with ventilation. The patient characteristics of these pneumonia cases are shown in Table 3. Cases of the three categories of pneumonia differed significantly by age, duration of ICU stay before onset of pneumonia, and the proportion of secondary sepsis and death. Patients with pneumonia associated with IMV were younger and had a longer ICU stay before onset of pneumonia than patients with pneumonia associated with NIV or patients without ventilation. Pneumonia cases associated with ventilation (IMV and NIV) had a higher proportion of secondary sepsis and death in comparison to pneumonia cases without ventilation, but there was no difference in this respect between the two modes of ventilation.

The proportion of cases with clinically defined pneumonia and with pneumonia with bacterial confirmation differed significantly between the three pneumonia categories ($P < 0.001$). Pathogens could be recovered in more patients with pneumonia undergoing IMV than in patients without ventilation or in patients receiving NIV. The numbers of cases of pneumonia associated with selected pathogens and their respective proportions per 100 pathogens are listed in Table 4. Pathogens are not listed by pneumonia cases, because due to the higher proportion of cases with isolated pathogens in the IMV pneumonia category, there was also a significantly higher proportion of nearly all specific pathogens in pneumonia associated with IMV.

Significant differences in the spectrum of associated pathogens per 100 pathogens were found for streptococci (higher proportion in pneumonia associated with NIV and in pneumonia not associated with ventilation), all gram-negative bacteria (higher proportion in ventilated patients) and *Pseudomonas aeruginosa* (higher proportion in ventilated patients). There were also significant differences ($P < 0.001$) in the duration from ICU admission to pneumonia for cases associated with different pathogens (data not shown). Especially pneumonia cases associated with *P. aeruginosa* showed a longer interval between ICU admission and pneumonia with a median duration of 12 days (NIV group) and 13 days (IMV group) in cases of pneumonia associated with *P. aeruginosa* compared to 9 days (NIV group) and 10 days (IMV group) in cases of pneumonia associated with other pathogens ($P = 0.036$).

Discussion

In this study we evaluated the incidence and the characteristics of three categories of nosocomial pneumonia—pneumonia associated with invasive mechanical ventilation, pneumonia associated with noninvasive mechanical ventilation and pneumonia not associated with ventilation—using data collected during continuous active surveillance in 400 German ICUs participating in the German nosocomial infection surveillance system.

Pneumonia associated with NIV has been difficult to characterize because it is a rare event and studies investigating pneumonia associated with NIV often include only few cases. A recent review that pooled data on pneumonia associated with NIV from 12 studies included a total of 38 cases with less than 10 pneumonia cases

Table 2 Utilization rate of ventilation and pneumonia incidence densities stratified by hospital size, hospital type and ICU type

Parameter	Utilization rate				Incidence density					
	NIV per 100 pd		IMV per 100 pd		Pneumonia associated with NIV per 1,000 NIV days		Pneumonia associated with IMV per 1,000 IMV days		Pneumonia not associated with ventilation per 1,000 pd (without NIV or IMV)	
	Median (Q1–Q3)	*P* value[a]	Median (Q1–Q3)	*P* value[a]	Median (Q1–Q3)	*P* value[a]	Median (Q1–Q3)	*P* value[a]	Median (Q1–Q3)	*P* value[a]
Total	2.4 (0.9–5.1)		35.4 (23.1–47.5)		0.0 (0.0–0.0)		4.7 (2.1–7.8)		0.1 (0.0–0.8)	
Hospital size										
≥600 beds	2.4 (1.1–5.6)		45.3 (35.6–56.0)		0.0 (0.0–0.0)		5.0 (2.4–8.6)		0.1 (0.0–0.7)	
<600 beds	2.4 (0.7–4.9)	0.260	28.2 (20.0–40.1)	<0.001	0.0 (0.0–0.0)	0.447	4.5 (1.7–7.6)	0.073	0.0 (0.0–1.0)	0.734
Hospital type										
University hospital	2.2 (0.5–5.7)		52.3 (40.3–62.9)		0.0 (0.0–0.0)		4.1 (1.9–7.2)		0.0 (0.0–0.7)	
Teaching hospital	2.6 (1.0–5.3)		37.8 (26.7–47.5)		0.0 (0.0–0.0)		5.0 (2.2–7.9)		0.2 (0.0–0.8)	
Other hospital	2.3 (0.6–5.0)	0.559	25.8 (19.0–37.3)	<0.001	0.0 (0.0–0.0)	0.374	4.7 (2.0–8.0)	0.789	0.0 (0.0–0.8)	0.200
ICU type										
Medical-surgical ICU	2.7 (0.9–5.4)		29.3 (20.1–41.4)		0.0 (0.0–0.7)		4.5 (1.9–7.6)		0.2 (0.0–0.8)	
Medical ICU	2.3 (0.6–4.8)		33.1 (25.3–44.0)		0.0 (0.0–0.0)		3.0 (1.3–5.8)		0.0 (0.0–0.5)	
Surgical ICU	1.9 (1.0–4.1)		41.2 (33.8–57.8)		0.0 (0.0–1.0)		6.6 (3.8–9.4)		0.0 (0.0–1.0)	
Other ICU	2.1 (0.5–8.7)	0.470	49.6 (34.0–58.0)	<0.001	0.0 (0.0–0.0)	0.094	5.9 (1.7–9.2)	<0.001	0.0 (0.0–0.9)	0.518

NIV noninvasive ventilation, *IMV* invasive mechanical ventilation, *pd* patient days, *Q1* 25% quantile, *Q3* 75% quantile

[a] Wilcoxon test for two categories and Kruskal-Wallis test for more than two categories

Table 3 Characteristics of 6,869 pneumonia cases that occurred in 400 KISS-ICUs between 2005 and 2007

Parameter	Pneumonia not associated with ventilation	Pneumonia associated with NIV	Pneumonia associated with IMV	Total	*P* value[a]
No. of pneumonia cases	898	160	5,811	6,869	
Age of patients, years, mean (±SD), median (IQR)	67.8 (±15.2), 71 (60–78)	69.2 (±14.5), 70.5 (64–80)	64.2 (±15.9), 68 (56–76)	64.8 (±15.8), 68 (57–79)	<0.001
Sex of patients, male, no. (%)	635 (70.7)	109 (68.1)	3,903 (67.2)	4,647 (67.7)	0.106
Time from ICU admission to pneumonia, days, mean (±SD), median (IQR)	10.8 (±13.3), 7 (4–13)	11.5 (±10.0), 8 (5–14)	15.4 (±31.4), 10 (6–18)	14.7 (±29.4), 9 (5–17)	<0.001
Cases diagnosed >4 days of ICU-admission, no. (%)	656 (73.1)	122 (76.3)	4,912 (84.5)	5,690 (82.8)	<0.001
Secondary sepsis, no. (%)	30 (3.3)	10 (6.2)	356 (6.1)	396 (5.8)	0.004
Death, no. (%)	128 (13.3)	34 (21.3)	1,052 (18.1)	1,214 (17.7)	0.009
Cases with no pathogens isolated, no. (%)	439 (48.9)	73 (45.6)	1,250 (21.5)	1,762 (25.7)	<0.001
Cases with pathogens isolated, no. (%)	459 (51.1)	87 (54.4)	4,561 (78.5)	5,107 (74.3)	<0.001
Pathogens recovered from[b]					
ETA, no. (% of pneumonia cases)	362 (40.3)	60 (37.5)	3,953 (68.0)	4,375 (63.7)	<0.001
BAL/PSB, no. (% of pneumonia cases)	114 (12.7)	26 (16.3)	1,037 (17.8)	1,177 (17.1)	0.001
Blood culture, no. (% of pneumonia cases)	47 (5.2)	6 (3.8)	392 (6.7)	445 (6.5)	0.084

No number, *IMV* invasive mechanical ventilation, *NIV* noninvasive ventilation, *SD* standard deviation, *IQR* inter-quartile range, *ETA* endotracheal aspirate, *BAL* bronchoalveolar lavage, *PSB* protected specimen brush

[a] Kruskal-Wallis or chi-square test

[b] Pathogens can be recovered from more than one type of material

reported in 11 of the 12 studies [18]. In this study we were able to document 160 cases of NIV-associated pneumonia using homogenous definitions, methods and criteria with the pooled data of 400 ICUs from a 3-year period. The low incidence of NIV-associated pneumonia is illustrated in our study by the fact that more than half of the participating ICUs did not document a single case of NIV-associated pneumonia during the analyzed period resulting in a median incidence density of 0 cases per 1,000 NIV days.

Our analysis shows that patient characteristics such as age and length of stay differed significantly between the analyzed categories of pneumonia cases. The finding that different patient populations might be affected by IMV- and NIV-associated pneumonia should be taken into account in the interpretation of studies regarding the benefit of NIV for prevention of pneumonia. Although patients receiving NIV in our study had the advantage of a reduced incidence of pneumonia, at the time they developed pneumonia the proportion of secondary sepsis and death was as high as in patients with IMV-associated pneumonia.

Pathogens were significantly more often recovered in patients with pneumonia associated with IMV, presumably due to the easier availability of material for culture, while more cases of pneumonia associated with NIV and pneumonia not associated with ventilation were diagnosed based on clinical findings only. The pathogens most often recovered in this study—*Staphylococcus aureus* and *Pseudomonas aeruginosa*—were the same as the ones most often reported to the NHSN system and in two large epidemiologic pneumonia studies [26–28]; however, starting from the third position, the composition of pathogens differs between the studies. Unfortunately, pathogens associated with pneumonia cases in our study cannot always be interpreted as causative or the only causative pathogens, because up to four pathogens could be reported per pneumonia episode. Especially *Candida* spp. are unlikely to play a large role as the cause of pneumonia.

The analysis of isolated pathogens showed significant differences in the spectrum of pathogens associated with the three pneumonia categories. However, it remains unclear whether these differences are directly related to the mode of ventilation or whether they are caused by differences regarding the patient population or the duration between ICU admission and onset of pneumonia in the three pneumonia categories. Especially the duration of ventilation prior to onset of pneumonia is known to influence the spectrum of isolated pathogens [29], and in our study there was significant variation in the interval between ICU admission and onset of pneumonia in the three groups. The differences in the spectrum of pathogens with for example a lower proportion of Streptococci and a higher proportion of gram-negative bacteria in the IMV group who has the longest interval between

Table 4 Selected pathogens associated with 6,869 cases of pneumonia reported from 400 ICUs between 2005 and 2007

	Pneumonia not associated with ventilation		Pneumonia associated with NIV		Pneumonia associated with IMV		All pneumonia cases		*P* value
	No.	Per 100 pathogens	No.	Per 100 pathogens	No.	Per 100 pathogens	No.	Per 100 pathogens	
Pneumonia cases total	898		160		5,811		6,869		
Pathogens total	722	100.0	137	100.0	6,789	100.0	7,648	100.0	
Gram-positive bacteria	196	27.1	42	30.7	1,783	26.3	2,021	26.4	0.418
Staphylococcus aureus	132	18.3	25	18.2	1,222	18.0	1,379	18.0	0.980
Thereof MRSA	49	6.8	5	3.6	443	6.5	497	6.5	0.379
Streptococcus spp.	21	2.9	6	4.4	102	1.5	129	1.7	**<0.001**
Gram-negative bacteria	386	53.5	76	55.5	4,009	59.1	4,471	58.5	**0.012**
Haemophilus spp.	21	2.9	0	0.0	194	2.9	215	2.8	0.132
Enterobacteriaceae	240	33.2	48	35.0	2,355	34.7	2,643	34.6	0.734
E. coli	83	11.5	17	12.4	665	9.8	765	10.0	0.224
Klebsiella spp.	75	10.4	14	10.2	690	10.2	779	10.2	0.982
Enterobacter spp.	39	5.4	9	6.6	450	6.6	498	6.5	0.446
Serratia spp.	14	1.9	3	2.2	187	2.8	204	2.7	0.408
Pseudomonas aeruginosa	86	11.9	25	18.2	1,067	15.7	1,178	15.4	**0.017**
Stenotrophomonas maltophilia	25	3.5	1	0.7	226	3.3	252	3.3	0.233
Acinetobacter spp.	12	1.7	1	0.7	152	2.2	165	2.2	0.305
Fungi	110	15.2	15	10.9	831	12.2	956	12.5	0.059
Candida spp.	81	11.2	13	9.5	634	9.3	728	9.5	0.262
Thereof *C.albicans*	59	8.2	8	5.8	523	7.7	590	7.7	0.641
Aspergillus spp.	5	0.7	0	0.0	84	1.2	89	1.2	0.189

Pathogens associated with pneumonia cases cannot always be interpreted as causative or the only causative pathogens, because up to four pathogens could be reported per pneumonia episode. Only the most common or most relevant pathogens are listed in the table

No number, *NIV* noninvasive ventilation, *IMV* invasive mechanical ventilation, *MRSA* methicillin-resistant *S. aureus*

admission and pneumonia are similar to the differences that have been described for early onset and late-onset pneumonia [23].

The reduced incidence of ventilator-associated pneumonia in patients receiving NIV in comparison to IMV has been attributed to the avoidance of endotracheal intubation. Endo-tracheal tubes have been shown to provide easy access for bacteria to the lower respiratory tract by impairing the mucociliary clearance and the cough reflex, providing a surface for biofilm formation and by facilitating microaspirations from the colonized oropharyngeal tract [30]. It has even been suggested that the term "endotracheal intubation related pneumonia" would be more appropriate than "ventilator-associated pneumonia" [31], and multiple prevention measures are focused on reducing the adverse effects of the endotracheal tube [32]. While in our study the mean pneumonia ID in patients receiving IMV was four times higher than for patients receiving NIV, our data also show that NIV is associated with a threefold increase of the pneumonia ID in comparison to no ventilation, suggesting that ventilation is associated with a higher risk for pneumonia also in the absence of the endotracheal tube.

A limitation of this study is that ICU-KISS does not collect data to describe the ICU patient population with regard to underlying diseases, disease severity or other known risk factors for nosocomial pneumonia, because it uses a unit-based and not a patient-based surveillance approach. For the same reason ICU-KISS does not collect data on the indication for and the duration of ventilation in individual patients. Structural data of ICUs can been used as a surrogate marker for different patient populations with for instance ICUs in larger or university hospitals in general caring for patients with higher disease severity. Contrary to this assumption, the analysis of structural data showed that only the ICU type and not the hospital size or the hospital type affected pneumonia IDs in patients receiving IMV. Surgical ICUs had significantly higher pneumonia IDs than the other ICUs confirming that surgical patients are a high-risk group for ventilator-associated pneumonia and should be targeted preferentially by prevention measures. This is in accordance with the finding that surgery itself—emergency surgery and elective surgery—is an independent risk factor for nosocomial pneumonia [33].

The use of NIV compared to IMV in this sample of ICUs seems to be low; however, the extent of documented NIV days might have been influenced by the strict criteria of at least 6 h of daily NIV use. Although it has been shown that NIV use has increased in response to published clinical research [34], 74 ICUs in our study did not document any NIV days, indicating that NIV has not been integrated systematically into practice in all ICUs. Patients in these ICUs might benefit from the education of

clinicians about noninvasive ventilatory strategies as recommended in guidelines [22].

In conclusion, this surveillance study demonstrates that surveillance of pneumonia associated with noninvasive ventilation is feasible in a large sample of 400 ICUs. Comparison of pneumonia associated with noninvasive ventilation to pneumonia associated with invasive ventilation and pneumonia not associated with ventilation shows significant differences of pneumonia incidence densities, patient characteristics and the spectrum of associated pathogens.

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Conflict of interest statement None.

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