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Clinical Spectrum of Ventilator-Associated Pneumonia Caused by Methicillin-Sensitive *Staphylococcus aureus*

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The incidence of tracheal colonization and its association with ventilator-associated pneumonia caused by methicillin-sensitive *Staphylococcus aureus* (MSSA) was studied prospectively in 530 consecutively admitted mechanically ventilated patients in a general intensive care unit. Furthermore, the clinical spectrum, outcome, and microbiological results of 27 cases of staphylococcal ventilator-associated pneumonia (SVAP) were examined. Ventilator-associated pneumonia was diagnosed by protected specimen brush and/or bronchoalveolar lavage. On admission, 7% of the patients were colonized with MSSA in the trachea. Acquired tracheal colonization was demonstrated in 10% of the patients and occurred less frequently in patients with a hospital stay of > 48 h before ICU admission compared to patients admitted directly to the ICU (6% vs. 15%, $p < 0.001$). Moreover, colonization was acquired more frequently among trauma and neurological/neurosurgical patients (22%) as compared to surgical and medical patients (7%) ($p < 0.0001$). Twenty-one patients (4%) developed SVAP, the incidence being higher in patients colonized in the trachea with MSSA than in those not colonized (21% vs. 1%, $p < 0.00001$). Staphylococcal ventilator-associated pneumonia developed more often in trauma and neurological/neurosurgical patients as compared to surgical and medical patients (8% vs. 3%, $p < 0.05$). Moreover, patients with a hospital stay of < 48 h before admission to the ICU had a higher incidence of SVAP as compared to those with a longer hospital stay before ICU admission (7% vs. 2%, $p < 0.01$). Crude infection-related mortality was 26%. Preceding colonization with MSSA in the trachea appears to be an important risk factor for the development of SVAP, and patients with a short duration of hospitalization before intensive care unit admission have the highest incidence of ventilator-associated pneumonia caused by MSSA.

Pneumonia is the most frequently occurring nosocomial infection among mechanically ventilated intensive care unit (ICU) patients (1), causing increased morbidity, mortality, and health care costs (2, 3). Due to its association with mechanical ventilation, this infection has also been called ventilator-associated pneumonia (VAP). Quite often, *Staphylococcus aureus* is the cause of VAP (1, 4). Although trauma and/or neurosurgical patients have been reported to be at greater risk of acquiring staphylococcal ventilator-associated pneumonia (SVAP) (5–8), the clinical presentation of staphylococcal pneumonia in mechanically ventilated patients has not been described in great detail. In contrast, several studies have investigated the clinical spectrum of community-acquired pneumonia caused by *Staphylococcus aureus*. The latter infection has been characterized as a rapidly developing, fulminating disease associated with high mortality, especially when complicating epidemic influenza (9, 10). In the UK *Staphylococcus aureus* was among the three pathogens

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Table 1: Number of patients analyzed and incidences of colonization and infection.

	Colonized on admission		Acquired colonization		Incidence of SVAP	
	Analyzed	Colonized	Analyzed	Colonized	Analyzed	Infected
Total	530	36 (7%)	485	48 (10%)	518	21 (4%)
Excluded for analysis	0		12 TAP+33 COA		12 TAP	
Surgery/medical patients	428		396	28 (7%)	418	13 (3%)
Trauma/neurological/ neurosurgical patients	102		89	20 (22%)	100	8 (8%)
Hospital stay before ICU admission > 48 h			266	15 (6%)	277	5 (2%)
Hospital stay before ICU admission < 48 h			219	33 (15%)	241	16 (7%)
Colonized (on admission or acquired)					81	17 (21%)
Not colonized					437	4 (1%)

COA, colonized on admission; TAP, topical antimicrobial prophylaxis; SVAP, staphylococcal ventilator-associated pneumonia.

identified as the most common causes of severe community-acquired pneumonia, with 100% mortality reported for cases caused by *Staphylococcus aureus* (11). In line with these observations, Fine et al. (12) found five risk factors associated with a complicated course in patients with community-acquired pneumonia, one of these being a pneumonia caused by a high-risk pathogen such as *Staphylococcus aureus*.

In the present study the incidence of colonization of the upper respiratory tract by MSSA and its association with the development of VAP caused by this species was determined in 530 mechanically ventilated ICU patients. In addition, the clinical spectrum and outcome of 27 patients with SVAP and the microbiological results are described. The diagnosis of VAP was established on the basis of positive quantitative cultures of samples obtained by protected specimen brush (PSB) and/or bronchoalveolar lavage (BAL). During the entire study period no methicillin-resistant *Staphylococcus aureus* (MRSA) was isolated.

Patients and Methods

Patients. From January 1992 through June 1994, tracheal colonization and development of VAP were studied prospectively in all mechanically ventilated patients in the general ICU of the University Hospital Maastricht, The Netherlands, in order to assess the incidence of colonization of the upper respiratory tract by MSSA and its association with the development of SVAP. Age, sex, APACHE II score, medical discipline of admission, and period of hospitalization before admission to the ICU were recorded for each patient on admission, and clinical parameters (vital signs, leukocytosis, temperature, etc.) were recorded daily. Colonization of the respiratory tract was monitored by culturing samples of tracheal aspirate on admission and, subsequently, at least twice weekly. Only patients needing mechanical ventilation with an ICU stay of at least three days were included in the final analysis.

To describe the clinical spectrum and outcome of SVAP, data on all cases of SVAP from January 1992 through June 1995 were collected prospectively as described above (n = 21). Because a study using topical antimicrobial decontamination of the oropharynx, which influences oropharyngeal colonization, was started in July 1994, data regarding tracheal colonization collected after this date were not used. However, data on the clinical spectrum and outcome of patients developing SVAP during this period were included (n = 6).

Definition of Colonization. Tracheal colonization was defined as the isolation of MSSA from tracheal aspirates without infection. Colonization on admission was established on the basis of a positive culture for MSSA obtained within 24 h after admission to the ICU. Colonization was considered acquired if there were cultures positive for MSSA from at least two consecutive samples but no colonization with MSSA on admission to the ICU.

Definition of Pneumonia. In case of clinical suspicion of pneumonia, bronchoscopy with PSB and BAL was performed. The diagnosis was established when (a) at least three of the following criteria were met: (i) rectal temperature > 38.0°C or < 35.5°C, (ii) blood leukocytosis (> $10.10^3/mm^3$) and/or left shift or blood leukopenia (< $3.10^3/mm^3$), (iii) more than 10 leukocytes per high-power field in Gram stain of tracheal aspirate, and (iv) a positive culture from tracheal aspirate, in combination with (b) a new or progressive infiltrate on chest radiograph and (c) the presence of (i) a positive quantitative culture of a sample of secretions obtained by BAL (cut-off point ≥ 10^4 cfu/ml) or PSB (cut-off point ≥ 10^3 cfu/ml), (ii) positive cultures from blood, or (iii) pleural fluid culture unrelated to another source and obtained within 48 h before and after respiratory sampling. The infection was considered ICU acquired if symptoms began at least 48 h after admission to the ICU (13).

Pneumonia was considered staphylococcal when caused by MSSA solely or, in case of a polymicrobial pneumonia, when quantitative cultures of MSSA were above the cut-off points for PSB and/or BAL or when this species was cultured from blood or pleural fluid.

Bronchoscopy. A fiberoptic bronchoscope (Pentax FB-15H/FB-15X, Pentax Medicals, Japan) was introduced

Table 2: Characteristics of patients included in the study.

Patient no.	Age (years)	Sex	Pre-existing disease	Reason for admission	Outcome
1	66	M	hypertension/COPD	ruptured aneurysm, abdominal aorta	S
2	17	M	none	trauma capitis	S
3	79	M	none	trauma thoracalis	D^1
4	28	M	drug and alcohol abuse	resuscitation	S
5	38	F	none	Myasthenia gravis	S
6	62	F	CVA/NIDDM/adenocarcinoma of sigmoid	resection of sigmoid	D^1
7	43	M	alcohol abuse	acute pancreatitis	D^3
8	54	M	amyloidosis/chronic renal failure/immunosuppressive drugs	amyloidosis/PCP	D^1
9	51	M	none	craniotomy	S
10	28	M	none	trauma thoracalis	S
11	91	F	none	trauma	D^3
12	66	F	none	status epilepticus	S
13	40	F	SLE/immunosuppressive drugs	acute renal failure	D^3
14	62	M	CAD/COPD	ruptured aneurysm, abdominal aorta	D^1
15	76	M	aortic aneurysm	trauma capitis/thoracalis	S
16	68	M	CAD/COPD	exacerbation of COPD	D^1
17	75	M	none	ruptured aneurysm, abdominal aorta	D^2
18	45	F	breast carcinoma/BMT	pneumonia due to CMV	D^3
19	71	M	oesophageal carcinoma/COPD	resection of oesophagus	D^2
20	40	F	epilepsy/Down's syndrome	resusciation after aspiration	S
21	77	M	CAD/adenocacinoma of colon	gastrointestinal bleeding	S
22	53	M	CAD	trauma capitis/thoracalis	S
23	72	M	Claudicatio intermittens/adenocarcinoma of rectum	resection recto-sigmoid	S
24	25	F	none	HELLP syndrome	S
25	24	M	none	trauma capitis	D^3
26	31	M	none	suicide attempt	S
27	67	F	hypertension	ruptured aneurysm, abdominal aorta	D^3

BMT, bone marrow transplantation; CAD, coronary artery disease; CMV, cytomegalovirus; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; D^1, death directly related to SVAP; D^2, death possibly related to SVAP; D^3, death not related to SVAP; HELLP syndrome, haemolysis, elevated liver function tests, low platelets syndrome; NIDDM, noninsulin-dependent diabetes mellitus; PCP, *Pneumocystis carinii* pneumonia; S, survived; SLE, systemic lupus erythematosus.

through a special adaptor (Swivel connector; Gibeck Respiration, Sweden) and advanced to the bronchial orifice of a lung segment containing a new or progressive infiltrate. A PSB (Microbiology brush; Mill-Rose Laboratories, USA) was then advanced to a wedged, peripheral position after dislodging the distal catheter plug to obtain lower airway secretions for microbiological analysis. After brushing, the bronchoscope was positioned in the adjacent subsegment and BAL was performed by infusing one aliquot of 20 ml of sterile saline (0.9% NaCl) followed by three aliquots of 50 ml. The liquid recovered after the first aliquot was discarded and the remaining lavage fluid was pooled. In all cases PSB was performed first. Bronchoscopy specimens were transported to the laboratory within 15 min of collection and analyzed within 1 h.

Microbiology. Cultures of tracheal aspirates were taken on the first day of admission and subsequently twice a week. Semiquantitative and quantitative microbiological analyses of the specimens were performed according to routine methods. Susceptibility to flucloxacillin, gentamicin, ciprofloxacin, and amoxicillin clavulanate was established by determination of the MICs by a microplate broth dilution method according to NCCLS criteria. *Staphylococcus aureus* ATCC 29213 was used as reference strain.

Mortality. Crude ICU mortality was defined as the percentage of patients dying during their ICU stay and crude hospital mortality as the percentage of patients dying during hospital stay. The crude infection-related mortality was defined as the percentage of patients who died and in whom any contribution of SVAP to the fatal outcome could not be excluded on clinical or histological grounds.

Statistical Analysis. Frequency comparisons were performed by chi-square test or Fisher's exact test. A probability value of < 0.05 was considered to denote statistical significance. Data are expressed as absolute numbers with percentages or as medians with ranges.

Results

Colonization and Infection by Methicillin-Sensitive Staphylococcus aureus. In the 30-month study period from January 1992 through June 1994, 530 mechanically ventilated patients were admitted to the ICU for at least three days. Twelve of these received topical antimicrobial prophylaxis of the oropharynx and stomach with antibiotics active against MSSA. Topical antimicrobial prophylaxis was started after the first culture samples had been obtained. The median age of the patients studied was 66 years (range 14–92) and the median duration of ICU stay eight days (range 3–349). Patients were surgical (n = 231, 43%), medical (n = 197, 37%), neurological, or neurosurgical (n = 56,

11%), or had been admitted because of multiple trauma (n = 46, 9%).

On admission, colonization of the upper respiratory tract with MSSA was observed in three of 12 patients receiving topical antimicrobial prophylaxis and in 33 of the remaining 518 patients (Table 1). Thus, 36 of 530 patients (7%) were colonized with MSSA on admission. Because the 12 patients receiving topical antimicrobial prophylaxis and the 33 colonized with MSSA on admission were excluded from analysis, data on acquired colonization of the upper respiratory tract with MSSA were evaluated in the remaining 485 patients (Table 1). Acquired colonization was demonstrated in 48 of these 485 patients (10%). Patients who had been hospitalized for longer than 48 h before admission to the ICU acquired colonization with MSSA less often than patients admitted directly to the ICU [15/266 (6%) vs. 33/219 (15%), $p < 0.001$]. Moreover, acquired colonization occurred more frequently among trauma and neurological/neurosurgical patients (20/89, 22%) than surgical and medical patients (28/396, 7%, $p < 0.0001$). The median ages of patients who did or did not acquire colonization were comparable: 67 years (range 17–88) and 66 years (range 14–92), respectively.

In the 30-month study period, 21 of 518 (4%) patients analyzed developed an episode of SVAP (Table 1). The incidence was higher among patients colonized in the trachea with MSSA [either present on admission (n = 33) or acquired during ICU stay (n = 48)]: 17 of 81 patients (21%) as compared to 4 of 437 patients not colonized (1%) developed SVAP ($p < 0.00001$). Staphylococcal VAP occurred more frequently in trauma and neurological/neurosurgical patients (8/100, 8%) than in surgical and medical patients (13/418, 3%) ($p < 0.05$), and patients hospitalized for less than 48 h before ICU admission had a higher incidence (16/241, 7%) compared to those with a longer duration of hospitalization before ICU admission (5/277, 2%) ($p < 0.01$).

Clinical Presentation and Outcome of Staphylococcal Ventilator-Associated Pneumonia. Reason for admission, sex, age, presence of pre-existing diseases, and outcome of the 21 patients who developed SVAP (described above) and of six patients who developed SVAP in the period from July 1994 through June 1995 are summarized in Table 2. The median age of the 27 patients was 54 years (range 17–91), the male/female ratio was 18/9, and the median APACHE II score was 18 (range 8–31). Fourteen patients had at least one pre-existing disease. Cardiovascular diseases were present in nine patients, respiratory diseases in four patients, and malignancies in five. Severe autoimmune disease and a combination of amyloidosis resulting in chronic renal failure and chronic use of immunosuppressive drugs were present in two additional patients.

The remaining 13 patients had no underlying disease before admission to the ICU, although two were known intravenous drug and/or alcohol abusers. These 13 patients were admitted because of multiple trauma (n = 5), acute pancreatitis (n = 1), neurological disease (n = 1), elective craniotomy (n = 1), resuscitation (n = 1), status epilepticus (n = 1), ruptured aneurysm of the abdominal aorta (n = 1) and hemolysis, elevated liver function tests, low platelets (HELLP) syndrome (n = 1). One patient was admitted because of a suicide attempt in which 10 ml of lampoil was injected intravenously.

In five patients (no. 2, 5, 9, 11, 14) MSSA was not cultured from tracheal aspirates on the day pneumonia was diagnosed. However, in patients 2 and 5, MSSA had previously been isolated from tracheal aspirates. Tracheal aspirate could not be obtained in patient 8 (Table 3).

The diagnosis of SVAP was based on positive quantitative cultures from both PSB and BAL in nine patients, once in combination with a positive blood culture. In 13 other patients the diagnosis was based on a positive quantitative culture from BAL only, and in three patients on a positive quantitative culture of PSB only. In the remaining two patients the diagnosis was made after positive blood cultures, in one patient in combination with positive cultures from pleural fluid. Three patients (no. 5, 6, 18) received systemic antimicrobial therapy at the time of bronchoscopy. Despite in vitro susceptibility of MSSA to these agents in two patients (no. 5, 18), quantitative cultures of PSB and BAL were above the cut-off points in both patients.

Ventilator-associated pneumonia seemed to be caused solely by MSSA in six patients (22%). In all other cases VAP was polymicrobial; among the species most frequently isolated in combination with MSSA were *Escherichia coli* (n = 7), *Haemophilus influenzae* (n = 6), *Pseudomonas aeruginosa* (n = 5), and *Klebsiella pneumoniae* (n = 4).

The duration of stay in ICU until SVAP was diagnosed ranged from 3 to 19 days (median, 9 days). Peak body temperatures ranged from 37.6°C to 40.9°C (median, 39.4°C) on the day of

Table 3: Microbiological diagnosis of the patients included in the study.

Patient no.	Tracheal aspirate	Protected specimen brush (cfu/ml)	Bronchoalveolar lavage (cfu/ml)	Blood	Pleural fluid
1	*Staphylococcus aureus* *Haemophilus influenzae*	not analyzed	*Staphylococcus aureus* (1×10^5) *Haemophilus influenzae* (1×10^5)	no growth	not analyzed
2	*Haemophilus influenzae* *Moraxella catarrhalis*	*Haemophilus influenzae* (1×10^4) *Staphylococcus aureus* (6×10^3)	*Haemophilus influenzae* (1×10^4) *Staphylococcus aureus* (3×10^3)	no growth	not analyzed
3	*Staphylococcus aureus* *Pseudomonas aeruginosa*	*Pseudomonas aeruginosa* (1×10^2)	*Staphylococcus aureus* (1×10^3) *Pseudomonas aeruginosa* (1×10^5)	*Staphylococcus aureus* *Pseudomonas aeruginosa*	*Staphylococcus aureus* *Pseudomonas aeruginosa*
4	*Staphylococcus aureus* *Streptococcus pneumoniae*	*Staphylococcus aureus* (4×10^3)	*Staphylococcus aureus* (2×10^4)	no growth	not analyzed
5	*Pseudomonas aeruginosa* *Escherichia coli*	*Pseudomonas aeruginosa* (1×10^4) *Escherichia coli* (2×10^2) *Staphylococcus aureus* (1×10^4)	*Pseudomonas aeruginosa* (2×10^4) *Staphylococcus aureus* (2×10^4)	not analyzed	not analyzed
6	*Staphylococcus aureus* *Pseudomonas aeruginosa*	*Staphylococcus aureus* (1×10^5) *Pseudomonas aeruginosa* (1×10^3)	*Staphylococcus aureus* (1×10^5) *Pseudomonas aeruginosa* (1×10^5)	no growth	not analyzed
7	*Staphylococcus aureus* *Klebsiella oxytoca*	*Staphylococcus aureus* (4×10^1) *Klebsiella pneumoniae* (1×10^1)	*Staphylococcus aureus* (2×10^4) *Klebsiella pneumoniae* (4×10^3) *Haemophilus influenzae* (1×10^5)	no growth	not analyzed
8	not analyzed	*Staphylococcus aureus* (1×10^4) *Escherichia coli* (4×10^3)	*Staphylococcus aureus* (6×10^3) *Escherichia coli* (9×10^2)	not analyzed	not analyzed
9	*Moraxella catarrhalis* *Pseudomonas aeruginosa*	not analyzed	*Moraxella catarrhalis* (1×10^7) *Pseudomonas aeruginosa* (2×10^5) *Staphylococcus aureus* (2×10^5)	no growth	not analyzed
10	*Staphylococcus aureus*	*Staphylococcus aureus* (9×10^2)	*Staphylococcus aureus* (5×10^4)	no growth	not analyzed
11	*Klebsiella pneumoniae*	*Klebsiella pneumoniae* (1×10^7) *Staphylococcus aureus* (1×10^7)	*Klebsiella pneumoniae* (1×10^7) *Staphylococcus aureus* (1×10^7)	*Klebsiella pneumoniae*	not analyzed
12	*Staphylococcus aureus* *Escherichia coli* *Candida albicans*	not analyzed	*Staphylococcus aureus* (1×10^5) *Escherichia coli* (1×10^5)	not analyzed	not analyzed
13	*Staphylococcus aureus* *Escherichia coli* *Klebsiella pneumoniae*	not analyzed	*Staphylococcus aureus* (1×10^5) *Escherichia coli* (1×10^5) *Klebsiella pneumoniae* (1×10^5)	*Klebsiella pneumoniae*	not analyzed
14	*Proteus mirabilis* *Enterococcus faecalis* *Candida albicans*	*Proteus mirabilis* (1×10^5) *Enterococcus faecalis* (1×10^5) *Enterobacter* spp. (5×10^2)	*Proteus mirabilis* (1×10^4) *Enterobacter* spp. (1×10^2) *Staphylococcus aureus* (1×10^4) *Klebsiella pneumoniae* (1×10^2)	not analyzed	*Enterococcus faecalis* *Klebsiella pneumoniae*
15	*Staphylococcus aureus*	not analyzed	*Staphylococcus aureus* (1×10^6) *Haemophilus influenzae* (1×10^6)	no growth	no growth
16	*Staphylococcus aureus* *Escherichia coli*	not analyzed	not analyzed	*Staphylococcus aureus* *Escherichia coli*	not analyzed
17	*Staphylococcus aureus* *Escherichia coli*	*Staphylococcus aureus* (1×10^5) *Escherichia coli* (1×10^5)	*Staphylococcus aureus* (1×10^5) *Escherichia coli* (1×10^5)	no growth	not analyzed
18	*Staphylococcus aureus*	not analyzed	*Staphylococcus aureus* (1×10^4)	no growth	not analyzed
19	*Staphylococcus aureus*	*Staphylococcus aureus* (8×10^2)	*Staphylococcus aureus* (3×10^4)	no growth	not analyzed
20	*Staphylococcus aureus* *Streptococcus pneumoniae* *Haemophilus influenzae*	*Staphylococcus aureus* (5×10^3) *Streptococcus pneumoniae* (1×10^7) *Haemophilus influenzae* (1×10^4) *Neisseria menengitidis* (1×10^4)	*Staphylococcus aureus* (1×10^6) *Streptococcus pneumoniae* (1×10^6) *Haemophilus influenzae* (1×10^6) *Neisseria meningitidis* (1×10^6)	no growth	not analyzed
21	*Staphylococcus aureus* *Haemophilus parainfluenzae*	*Staphylococcus aureus* (1×10^5)	*Staphylococcus aureus* (1×10^5)	no growth	not analyzed
22	*Staphylococcus aureus* *Streptococcus agalactiae*	*Staphylococcus aureus* (1×10^3)	*Staphylococcus aureus* (4×10^3)	no growth	not analyzed
23	*Staphylococcus aureus* *Pseudomonas aeruginosa* *Enterococcus faecalis* *Klebsiella oxytoca*	not analyzed	*Staphylococcus aureus* (1×10^5) *Pseudomonas aeruginosa* (1×10^6) *Escherichia coli* (1×10^4)	*Staphylococcus aureus*	not analyzed
24	*Staphylococcus aureus*	*Staphylococcus aureus* (4×10^3)	*Staphylococcus aureus* (1×10^5)	*Staphylococcus aureus*	not analyzed
25	*Staphylococcus aureus* *Haemophilus influenzae*	*Staphylococcus aureus* (1×10^5) *Haemophilus influenzae* (1×10^4)	*Staphylococcus aureus* (2×10^4) *Haemophilus influenzae* (1×10^3)	not analyzed	not analyzed
26	*Staphylococcus aureus*	*Staphylococcus aureus* (2×10^2)	*Staphylococcus aureus* (1×10^5)	no growth	not analyzed
27	*Staphylococcus aureus*	*Staphylococcus aureus* (5×10^2)	*Staphylococcus aureus* (1×10^5)	no growth	not analyzed

diagnosis. Two patients had normal body temperature, but one of these (no. 8) was treated with high doses of immunosuppressive drugs. The leukocyte count ranged from 3.6 x 10^9/l to 31.5 x 10^9/l (median, 15.7 x 10^9/l), and in four patients more than five immature granulocytes were present in the differential count.

In all, 13 of 27 patients died during their hospital stay (crude hospital mortality, 48%), 11 of whom died during ICU stay (crude ICU mortality, 41%). The number of days between the diagnosis of SVAP and death ranged from 1 to 65 (median, 13). The episode of SVAP was unlikely to have directly influenced the fatal outcome in six patients. Four of these six patients died 37, 42, 50, and 65 days after the diagnosis of SVAP had been established, of cardiac failure (n = 2), septicemia due to endocarditis caused by another microorganism (n = 1), and septicemia from an abdominal source with intestinal microorganisms (n = 1). In the remaining two patients signs of bacterial pneumonia were no longer present at autopsy (1 patient died 11 days after SVAP was diagnosed due to septicemia caused by *Staphylococcus epidermidis*: the other patient, admitted because of head trauma, died 7 days after SVAP was diagnosed due to severe cerebral damage resulting from the initial trauma).

Staphylococcal VAP seemed to be directly related to death in five patients (no. 3, 6, 8, 14, 16). These patients died within six days after SVAP had been diagnosed, except patient no. 8, who died after 13 days (signs of pneumonia were still obvious at autopsy). Patient 19 died because of recurrent episodes of VAP 46 days after the first episode, which was caused by MSSA, had been diagnosed. In addition, patient 17 also suffered from secondary peritonitis and eventually died of multiple organ failure. The contribution of SVAP to the fatal outcome in these two cases, therefore, could not be excluded. Thus, SVAP was unrelated to mortality in six patients and seemed to be directly related in five patients; SVAP was possibly related to mortality in two patients. As a result the crude infection-related mortality in the 27 patients with SVAP was 26% (7/27).

A closer look at these patients reveals some interesting findings. Nine patients were ≤ 55 years and were admitted without pre-existing diseases. The mortality in this subgroup of patients was 22%; two of these patients died (no. 7 and 25). Death of both patients seemed unrelated to SVAP: patient 7, admitted with severe necrotizing pancreatitis, died in cardiac arrest without suspicion of infection 50 days after pneumonia had been diagnosed; patient 25 died seven days after pneumonia was diagnosed because of severe cerebral damage following the head trauma for which he was admitted, and signs of bacterial pneumonia were no longer present at autopsy. In contrast, three of five patients ≤ 55 years but with severe pre-existing diseases died during their ICU stay (no. 8, 13, 18), and in two of these patients (no. 13 and 18) pneumonia was unlikely to have influenced the outcome. Of the remaining 13 patients, all > 55 years of age, eight (62%) died, and five of these deaths seemed to be related directly to the development of SVAP. The relationship between age and crude infection-related mortality of SVAP showed a trend towards significance (Fisher's exact test p = 0.09).

Staphylococcal VAP was accompanied by empyema in two (7%) patients (no. 4 and 14), and cavitation was suspected on chest radiograph and confirmed by computer tomographic scanning in one (4%) patient (no. 13). A recurrent episode of VAP occurred in six patients: in five cases caused by *Pseudomonas aeruginosa* and in one by *Citrobacter freundii*.

In the group of six patients in whom VAP was caused by MSSA alone, three (50%) died. Death was directly related to SVAP in two cases and possibly related in one case.

All cultured isolates of *Staphylococcus aureus* were methicillin sensitive. All patients except patient 14 were treated with antibiotics active against MSSA. Amoxicillin clavulanate (n = 7) and flucloxacillin (n = 6) were used most frequently as monotherapy but were used in combination with gentamicin in two and three patients, respectively. Because of concomitant infections, polymicrobial VAP, or the presence of a prosthesis, the remaining eight patients were treated with various combinations of antibiotics: ticarcillin clavulanate (n = 2), ticarcillin clavulanate plus gentamicin (n = 1), amoxicillin (n = 1; because of penicillin-sensitive MSSA), cefuroxime plus gentamicin (n = 1), teicoplanin plus gentamicin (n = 1), vancomycin (n = 1), or vancomycin plus ceftazidime (n = 1). Patient 14 died on the day the definitive culture results of PSB and BAL were available and before antibiotic therapy active against penicillin-resistant MSSA was started. This patient died while receiving piperacillin for pleural empyema and fluconazole for tracheitis.

Discussion

The main feature of this study is that the clinical spectrum of VAP in which MSSA has an etiological role differs markedly from the well-known fulminating community-acquired pneumonia caused by this pathogen. Ventilator-associated pneumonia caused by MSSA was polymicrobial in most cases (78%) and had a rather mild clinical presentation. However, despite these findings, the overall mortality of patients developing this infection was almost 50%, with a crude infection-related mortality of 26%. Prior colonization with MSSA in the trachea appears to be an important risk factor, and patients with a short duration of hospitalization before ICU admission had the highest incidence of SVAP.

In the present study the median day of admission to the ICU on which SVAP was diagnosed was day 9. Therefore, the cases of VAP described here cannot be considered as early-onset pneumonia, which is defined as pneumonia occurring in the first four days of mechanical ventilation and which is most frequently caused by species already colonizing the upper respiratory tract before admission to the ICU (14). In a previous study performed in the same ICU and using the same diagnostic methods, MSSA was the most important pathogen associated with VAP, after *Pseudomonas aeruginosa* (15). In that study the overall incidence of VAP was 22%, and MSSA was involved in 35% of the cases (15). This incidence of pneumonia is comparable to the incidences reported by others using the same diagnostic techniques (4).

The clinical course of SVAP in the present study was associated with elevated body temperatures and leukocyte counts, a finding not surprising given that both are diagnostic criteria. However, more severe presentations such as septicemia, pleural involvement, and abscess formation developed in only one patient each. In addition, other infection parameters were observed infrequently: only four patients had more than five immature leukocytes in the differential cell count, and no patient developed leukopenia. The rather mild presentation of nosocomial pneumonia is in contrast to the well-known clinical picture of fulminating community-acquired pneumonia due to MSSA, especially in those recovering from influenza (9). This rapidly progressive infection has been associated with high incidences of cavitation (25%) and empyema (10%) (9). Moreover, the clinical presentation as described in the present study is also incompatible with the clinical course of MSSA pneumonia described by Kaye et al. (16), who found "an infection typical of a severe bacterial infection, with high fevers and usually significant leukocytosis, and positive blood cultures in a third of the patients". However, these data are difficult to compare to ours, because among the patients studied by Kaye and colleagues (16), 20% had community-acquired pneumonia and the number of patients requiring mechanical ventilation was not specified.

Besides the differences in clinical presentation, two other characteristics of SVAP deserve attention. First, there seems to be a difference between the patient population developing SVAP and that developing community-acquired pneumonia due to MSSA. Community-acquired pneumonia due to MSSA develops in particular in elderly patients, notably following a viral infection of the respiratory tact (9, 17). In contrast, SVAP more frequently affects young adults who have been hospitalized for a short period before admission to the ICU, such as patients admitted because of trauma or neurological/neurosurgical pathology. We found that these patients were also at risk for staphylococcal colonization, which is an important risk factor for the development of SVAP. These observations confirm the very few data available on the epidemiology of SVAP. For instance, Espersen and Gabrielsen (5) reported a higher incidence of nosocomial pneumonia due to *Staphylococcus aureus* among neurosurgical patients (25.9%) as compared to other patients (1.2%). In keeping with these results, Rello et al. (6, 7) demonstrated that staphylococcal pneumonia was associated with coma, age < 25 years, the nonuse of steroids, and preceding trauma. In another study VAP caused by MSSA occurred more frequently in patients with craniocephalic trauma, whereas VAP due to methicillin-resistant *Staphylococcus aureus* more frequently affected patients who had received steroids, had been ventilated for more than six days, had preceding chronic obstructive pulmonary disease, or were older than 25 years (8). Moreover, previous antibiotic therapy appeared to be the most important risk factor for developing VAP caused by methicillin-resistant *Staphylococcus aureus* (8). The results of these studies suggest that patients with a short duration of hospitalization prior to ICU admission are especially prone to develop SVAP, and that this infection is frequently preceded by tracheal colonization with *Staphylococcus aureus*. In theory, colonization of the nares with *Staphylococcus aureus* on admission to ICU might have been present in these patients. For reasons as yet unknown, nasal colonization

may spread to tracheal colonization and cause pneumonia. This theory needs further exploration.

In contrast to VAP caused by MSSA, infections caused by methicillin-resistant *Staphylococcus aureus* have all the characteristics of ICU-acquired infections. Fortunately, methicillin-resistant *Staphylococcus aureus* is not endemic in the Netherlands. The prevalence was 0% in the European Prevalence of Infection in Intensive Care (EPIIC) study (18, 19), and no episode of VAP caused by methicillin-resistant *Staphylococcus aureus* has occurred in our hospital to date. A second difference between the two forms of staphylococcal infection may be that VAP is often polymicrobial (78% in the present study). *Pseudomonas aeruginosa* and *Enterobacteriaceae* were the pathogens most frequently isolated, together with MSSA. This is in accordance with the bacterial flora known to colonize the upper and lower respiratory tract of long-term, mechanically ventilated ICU patients (20). The polymicrobial etiology of VAP has drawn little attention, although high incidences have been reported in the literature (21–24). In an experimental model Johanson et al. (20) investigated nosocomial pneumonia in baboons receiving prolonged mechanical ventilation. For the diagnosis they used cultures of lung homogenates and histologic findings as gold standards. In this model pneumonia was found to be polymicrobial in all cases.

Despite the relative benign clinical presentation of SVAP and the availability of effective antibiotics, the overall mortality was 48% in the present study and the crude infection-related mortality 26%. Although the data of this study cannot answer the question of whether a patient died of or with pneumonia, the data do suggest that in young patients, pre-existing diseases rather than pneumonia itself determined the outcome. In contrast, in patients over age 55, four of the eight patients who died succumbed within six days after pneumonia had been diagnosed. This finding corroborates the alleged relationship between VAP and mortality as reported by Fagon et al. (3) and by Kappstein et al. (2).

In conclusion, the results of the present study demonstrate that in most patients SVAP is not a fulminating disease. In many cases the infection is polymicrobial, and patients with a short duration of hospitalization before ICU admission seem to be especially prone to this infection.

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