Intensive Care Med (2007) 33:1533–1540
DOI 10.1007/s00134-007-0619-x

ORIGINAL

Elpis Giantsou
Nikolaos Liratzopoulos
Eleni Efraimidou
Maria Panopoulou
Eleonora Alepopoulou
Sofia Kartali-Ktenidou
Konstantinos Manolas

De-escalation therapy rates are significantly higher by bronchoalveolar lavage than by tracheal aspirate

Received: 19 August 2006
Accepted: 5 March 2007
Published online: 5 June 2007

E. Giantsou · N. Liratzopoulos ·
E. Efraimidou · K. Manolas
Demokritus University of Thrace, Intensive Care Unit, Department of Surgery, Medical School,
University Campus, 68100 Alexandropolis, Greece
e-mail: kmanolas@med.duth.gr

M. Panopoulou · E. Alepopoulou ·
S. Kartali-Ktenidou
Demokritus University of Thrace, Department of Microbiology Medical School,
University Campus, 68100 Alexandropolis, Greece
e-mail: skartali@med.duth.gr

E. Giantsou (✉)
Electras 10,
Marousi, 15122 Athens, Greece
e-mail: elpisgiantsou@yahoo.com
Tel.: +30-2-102824447
Fax: +30-2-102824447

Abstract *Objective:* To assess outcomes with de-escalation therapy in ventilator-associated pneumonia (VAP). *Design:* Prospective observational study. *Setting:* Multidisciplinary intensive care unit. *Patients and participants:* VAP was diagnosed by positive quantitative cultures of both tracheal aspirate and bronchoalveolar lavage (BAL) and treated appropriately for all significant isolates of tracheal aspirate and BAL in 143 patients who were assigned to de-escalation therapy by BAL or tracheal aspirate. *Interventions:* None. *Measurements and results:* Antibiotic therapy was de-escalated in 58 patients (40.5%), who had decreased mortality at day 15 (5.1% vs. 31.7%) and day 28 (12% vs. 43.5%) and shorter intensive care unit (17.2 ± 1.2 vs. 22.7 ± 6.3 days) and hospital (23.7 ± 2.8 vs. 29.8 ± 11.1 days) stay ($p < 0.05$). Of the 81 patients assigned to tracheal aspirate, the 17 (21%) who achieved de-escalation of therapy had reduced 15-day mortality (5.8% vs. 34.3%), reduced 28-day mortality (11.6% vs. 45.3%), and shorter intensive care unit (17.2 ± 1.6 vs. 22.4 ± 6.4 days) and hospital (23.1 ± 4.4 vs. 29.9 ± 11.1 days) stay ($p < 0.05$). Of the 62 patients assigned to BAL, the 41 (66.1%) who achieved de-escalation of therapy had decreased 15-day mortality (4.8% vs. 23.8%), decreased 28-day mortality (12.1% vs. 38%), and shorter intensive care unit (17.2 ± 1.1 vs. 23.2 ± 6 days) and hospital (23.8 ± 2.4 vs. 29.8 ± 11.4 days) stay ($p < 0.05$). *Conclusions:* For patients with VAP who have had appropriate treatment and shown a favorable clinical response, mortality and duration of stay can be further improved by de-escalation therapy.

Keywords De-escalation therapy · Ventilator-associated pneumonia

Introduction

Antibiotic therapy of patients with ventilator-associated pneumonia (VAP) is now regarded as a two-stage process [1–3]. The first stage involves administering broad-spectrum antibiotics to avoid inappropriate treatment in patients with true bacterial pneumonia. The second stage involves de-escalating an initially appropriate antibiotic regimen to avoid overuse of antibiotics, by streamlining, shortening or stopping therapy, as dictated by the patient's clinical response and information about the bacteriology of the infection. Although de-escalation therapy is suggested to be part of any appropriate antimicrobial stewardship in patients with VAP [3], controversy continues regarding the outcomes associated with its implementation. Indeed, some reports suggest that de-escalation therapy does not affect mortality and duration of intensive care unit (ICU) and hospital stay [4, 5], whereas others claim that it does significantly improve them [6, 7]. Moreover, there are suggestions that de-escalation therapy improves mortality at 2 weeks after VAP onset, but does not significantly affect either mortality at 1 month or the duration of ICU

and hospital stay [8]. However, the potential effect of de-escalation therapy on outcomes, that are based on clinical diagnosis of VAP, may be difficult to assess, as clinical diagnosis is frequently associated with risk for overestimation of the incidence of infection [9, 10]. Therefore, the objective of this study was to assess outcomes in association with the implementation of de-escalation therapy in a well-defined group of patients [11] who had developed VAP as confirmed by two separate cultures, one quantitative tracheal aspirate and one bronchoalveolar lavage (BAL) sample, that both had to be positive.

Materials and methods

Study design and patients

The study was conducted during a 24-month period at the University of Thrace teaching hospital (500 beds), Greece. Patients were entered into the study if: (a) they were older than 18 years of age and (b) their physicians established a diagnosis of VAP. Patients were excluded if they (a) were temporarily transferred to our ICU due to lack of available beds in another hospital, (b) had received solid organ or bone marrow transplant or (c) had human immunodeficiency virus infection. The study was approved by the local human studies ethics committee, and informed consent was obtained as appropriate.

The initial antibiotic regimen was de-escalated when the patient's clinical response and the microbiological information permitted. The clinical response was decided at 72 h reassessment by absolute consensus of five attending physicians after a clinical round. The microbiological information that the attending physicians used to de-escalate antibiotic therapy, to establish the appropriateness of the initial antibiotic regimen and to confirm the diagnosis of VAP, in patients with clinical suspicion for infection, was derived from quantitative tracheal aspirate or BAL. Nevertheless, because the aim of the study was to assess outcomes with de-escalation therapy and not to evaluate the contribution of different methods to diagnosis, we studied only patients in whom the diagnosis of VAP was confirmed by both quantitative tracheal aspirate and BAL samples, and who received an appropriate empiric antibiotic regimen for all isolates of tracheal aspirate and BAL that reached significant concentration. Data interpretation was performed by two independent investigators and the attending physicians were blind to the nature of the study. Patients could not be entered more than once into the study, and only the first VAP episode for each patient was considered.

The type of respiratory sample that guided de-escalation therapy, quantitative tracheal aspirate or BAL, was determined by the availability of services. A respiratory sample collection kit (tracheal aspirate or BAL) was delivered to ICU every 12 h and was assigned to the first patient in need. Using the kit assigned to the case, the attending physicians collected the respiratory sample within 12 h after clinical suspicion for VAP was raised. Patients in whom a kit other than the assigned kit was used were not studied. However, all patients had both types of samples, because, within 2 h after the collection of tracheal aspirate or a BAL sample by the attending physicians, the other type of sample was collected by two independent investigators before any antibiotic introduction or modification. The empiric antibiotic regimen was started as soon as both samples, tracheal aspirate and BAL, had been collected.

Tracheal aspirates and BAL were both cultured with quantitative technique. The clinical suspicion for VAP was raised according to predefined criteria [12]. Late-onset VAP was developed after at least 7 days of mechanical ventilation [13].

De-escalation therapy

De-escalation therapy was defined as either the switch to an agent that was less broad spectrum than initial therapy, or the use of fewer drugs [14]. Thus it was possible to have either or both types of antibiotic changes in a given patient. The use of fewer drugs involved stopping oxazolidinone when MRSA was not grown, and aminoglycoside or quinolone when *P. aeruginosa* was not identified. The empiric antibiotic regimen was guided by the Gram stain, the presence of risk factors for multiresistant pathogens and the local microbiology data [15]. Antibiotics were ranked according to activity spectrum against Gram-negative bacteria (highest 4, lowest 1) as follows [6, 13]: carbapenems 4; extended spectrum penicillins 3, quinolone and aminoglycoside 2, and beta-lactams 1 [16]. This rank of activity spectrum was used to de-escalate therapy to the narrowest spectrum agent available. In the absence of *P. aeruginosa*, carbapenem was de-escalated to extended-spectrum penicillin, or to quinolone, or if possible to a non-antipseudomonal beta-lactam, and extended-spectrum penicillin was de-escalated to quinolone or if possible to a non-antipseudomonal beta-lactam. In the presence of *P. aeruginosa*, de-escalation therapy was as above but, the final regimen had to include two antipseudomonal drugs. Therefore, in this case carbapenem was de-escalated to extended-spectrum penicillin or to a antipseudomonal beta-lactam, and extended-spectrum penicillin to an antipseudomonal beta-lactam, while quinolone or aminoglycoside was continued as part of the combination regimen.

Patient flow

During the study period clinical suspicion for VAP was raised in 459 patients, of whom 331 (72.1%) were diag-

nosed with VAP by two positive cultures, one quantitative tracheal aspirate and one BAL. Of these, 236 (51.4%) had received appropriate initial treatment, confirmed by both tracheal aspirate and BAL, and demonstrated favorable clinical response. The first available respiratory sample collection kit, tracheal aspirate or BAL, was used to collect the sample that guided de-escalation therapy in 156 (33.9%) patients, of whom 143 (31.1%) had de-escalation therapy according to the predefined protocol and finally constituted the study population.

Data collection and end points

On admission the following variables were recorded: age, gender, Simplified Acute Physiologic Score (SAPS) II [17], Sequential Organ Failure Assessment (SOFA) score [18], admission category (medical versus surgical, elective versus emergency surgical), origin (medical or surgical ward versus home) indication for mechanical ventilation and predicted mortality according to SAPS II. At collection of respiratory samples, the following baseline variables were recorded: previous duration of mechanical ventilation, use of antimicrobials 15 days before VAP, temperature in °C, white blood cell count per mm^3, ratio of partial pressure of arterial oxygen to fraction of inspired oxygen (PaO_2/FiO_2), and presence of respiratory, cardiovascular, renal, neurological, hepatic and/or hematological dysfunction [19].

Before de-escalation of antibiotics we recorded the initial empiric regimen and the pathogens recovered at significant concentrations at the respiratory specimen that guided de-escalation therapy.

The primary end point was to assess outcomes with de-escalation therapy, in patients with VAP, as confirmed by two separate positive cultures, one quantitative tracheal aspirate and one BAL. Secondary end points were to evaluate outcomes with de-escalation therapy guided by BAL and by quantitative tracheal aspirate.

Statistical analysis

Descriptive analysis was performed. The number of organisms recovered from tracheal aspirate and BAL cultures was expressed as colony-forming units/ml. All other results were expressed as mean ± standard deviation (SD) or as percentages of total values. Frequencies were compared by means of a chi-square test with Yates correction or Fisher's exact test when appropriate. Student's *t*-test was used to compare the means of BAL and tracheal aspirate groups. All *p*-values were two sided and considered significant when they were less than 0.05.

Table 1 Admission characteristics of 143 patients with ventilator-associated pneumonia as a function of the de-escalation therapy status

Characteristics	De-escalation therapy ($n = 58$)	No de-escalation therapy ($n = 85$)	*p*-value
Age, mean (SD), years	65 (10.6)	63.7 (7.7)	0.4
Men, no. (%)	38 (65.5)	56 (65.8)	0.9
Diagnostic score, mean (SD)			
SAPS II	44.7 (10.2)	43.8 (10.2)	0.6
SOFA	7.1 (1.09)	7.1 (1.1)	0.9
Admission category, no. (%)			
Medical	34 (58.6)	49 (57.6)	0.9
Emergency surgery	10 (17.3)	17 (20)	0.6
Elective surgery	14 (24.1)	19 (22.4)	0.8
Origin, no. (%)			
Medical or surgical ward	46 (79.3)	67 (78.8)	0.8
Home	12 (20.7)	18 (21.2)	0.9
Indication for MV, no. (%)			
ARDS	3 (5.2)	5 (5.9)	0.8
Status asthmaticus	3 (5.2)	8 (9.4)	0.5
COPD exacerbation	8 (13.8)	12 (14.1)	0.9
Community-acquired pneumonia	9 (15.5)	13 (15.4)	0.9
Drug overdose	8 (13.8)	11 (12.9)	0.8
Abdominal surgery	7 (12.1)	7 (8.2)	0.4
Surgery other than abdominal	4 (6.9)	4 (4.7)	0.5
Congestive heart failure	6 (10.3)	3 (3.5)	0.09
Neurological emergency	10 (17.2)	22 (25.9)	0.2
Predicted mortality, no. (%)	19 (32.7)	27 (31.7)	0.9

SAPS II, Simplified Acute Physiologic Score II; *SOFA*, Sequential Organ Failure Assessment; *MV*, mechanical ventilation; *ARDS*, adults respiratory distress syndrome; *COPD*, chronic obstructive pulmonary disease

Results

Characteristics of the patients

A total of 143 patients with VAP were prospectively evaluated. The mean age was 64.2 (± 9) years; 94 (68.5%) were men. The mean SAPS II and SOFA score on admission were 44.2 (± 10.2) and 7.1 (± 1.1) respectively. VAP was late-onset in 101 (70.6%) of cases. The case mix was medical in 58%, emergency surgery in 18.9% and elective surgery in 23.1%. De-escalation of antibiotic therapy was accomplished in 58 (40.5%) patients. No significant differences were noted between patients in whom therapy was de-escalated and those in whom it was not, in admission (Table 1) and baseline (Table 2) characteristics, in antibiotics initially prescribed (Table 3) and in pathogens identified at significant concentrations in the sample (quantitative tracheal aspirate or BAL) that guided de-escalation therapy (Table 3).

Table 2 Baseline characteristics of 143 patients with ventilator-associated pneumonia as a function of the de-escalation therapy status

Characteristics	De-escalation therapy ($n = 58$)	No de-escalation therapy ($n = 85$)	p-value
MV duration before VAP, mean (SD), days	7.5 (1.7)	7.8 (1.5)	0.3
Antimicrobials 15 days before VAP, no. (%)	46 (79.3)	65 (76.4)	0.6
Temperature, °C, mean (SD)	39.4 (0.5)	39.5 (0.5)	0.6
Leukocyte count, mean (SD), µl	16,948 (1898)	16,684 (1760)	0.3
PaO_2/FiO_2, mean (SD), mmHg	220.4 (17.3)	218.5 (16.2)	0.5
Organ/system failure*			
Respiratory	36 (62)	55 (64.7)	0.7
Cardiovascular	15 (25.8)	25 (29.4)	0.6
Renal	4 (6.8)	3 (3.5)	0.4
Central nervous	16 (27.5)	35 (41.1)	> 0.05
Hepatic	4 (6.8)	4 (4.7)	0.7
Coagulation	2 (3.4)	2 (2.2)	> 0.05

VAP, ventilator-associated pneumonia; *MV*, mechanical ventilation; PaO_2/FiO_2, ratio of partial pressure of arterial oxygen to fraction of inspired oxygen; * Organ/system failure was considered present when the corresponding Sequential Organ Failure Assessment score was > 2. The percentages do not always add up to 100 as more than one organ/system failure can occur

Table 3 Antibiotics initially prescribed and pathogens identified in the respiratory sample that guided de-escalation therapy decisions in 143 patients with ventilator-associated pneumonia

	De-escalation therapy ($n = 58$)	No de-escalation therapy ($n = 85$)	p-value
Antibiotic			
Carbapenem	32 (55.1)	49 (57.6)	0.7
Aminoglycoside	22 (37%)	26 (30.5)	0.3
Extended spectrum penicillin	26 (44.8%)	27 (31.7)	0.1
Quinolone	36 (62%)	50 (58.8)	0.6
Oxazolidinone	32 (55.1)	34 (40)	0.07
Pathogens			
Bacilli			
P. aeruginosa	29 (50)	47 (55.2)	0.5
Escherichia coli	5 (8.6)	9 (10.5)	0.6
Proteus	5 (8.6)	6 (7)	0.7
Serratia	5 (8.6)	11 (12.9)	0.4
Klebsiella	10 (17.2)	16 (18.8)	0.8
Morganella morganii	4 (6.8)	5 (5.8)	> 0.05
Haemophilus influenzae	9 (15)	14 (16.4)	0.8
Cocci			
MRSA	11 (19)	27 (31.7)	0.08
MSSA	12 (20.6)	8 (9.4)	> 0.05
Other cocci	9 (15.5)	7 (8.1)	0.1

MRSA, methicillin-resistant *Staphylococcus aureus*; *MSSA*, methicillin-sensitive *Staphylococcus aureus*; * Values are given as *n* (%); percentages represent patients who initially received the antibiotics presented and in whom were isolated at significant concentrations the pathogens presented, in the quantitative tracheal aspirate or bronchoalveolar lavage sample, that guided de-escalation therapy decisions. Percentages may not add up to 100 because of combination multi-drug regimens and isolates with more than one pathogen grown at significant concentration

End points

Patients in whom antibiotic therapy was de-escalated, compared with those in whom it was not, had reduced 15-day and 28-day mortality (Table 4). Of the 62 patients who were assigned to BAL, 41 (66.1%) achieved de-escalation of antibiotic therapy and, compared with those who did not, despite their similar assignment, had significantly reduced 15-day and 28-day mortality (Table 4). Similarly, of the 81 patients who were assigned to quantitative tracheal aspirate, 17 (21%) achieved de-escalation of antibiotic therapy and, compared with those who did not, despite their similar assignment, had reduced 15-day and 28-day mortality (Table 4).

Patients who achieved de-escalation of therapy had shorter duration of stay in ICU and in hospital than those who did not (Table 4). Patients assigned to BAL or quantitative tracheal aspirate in whom treatment was de-escalated, compared with those in whom it was not, despite their similar assignment, had significantly shorter duration of stay in ICU and hospital (Table 4). Survivors in whom treatment was de-escalated, compared with those in whom it was not, had shorter duration of stay in ICU (17.4 ± 1.1 vs. 26.7 ± 3.3, $p < 0.05$) and in hospital (25.6 ± 4.3 vs. 36.73 ± 4.8, $p < 0.05$).

The whole group of patients assigned to BAL, those who achieved de-escalation of therapy and those who did not, compared with the whole group of those assigned to quantitative tracheal aspirate, had reduced 15-day mortality (11.29% vs. 28.39%, $p = 0.01$), reduced 28-day mortality (20.96% vs. 38.27%, $p = 0.02$) and fewer days in ICU (19.2 ± 4.6 vs. 21.4 ± 6.1, $p = 0.01$) and in hospital (25.8 ± 7.4 vs. 28.4 ± 10.4, $p = 0.08$). No significant differences in mortality at day 15 and day 28 or in duration

Table 4 Study outcomes as a function of the de-escalation therapy status

Primary end point	De-escalation therapy ($n = 58$)	No de-escalation therapy ($n = 85$)	p-value
Death from all causes at 15 days, *n* (%)	3/58 (5.1)	27/85 (31.7)	< 0.05
Quantitative tracheal aspirate	1/17 (5.8)	22/64 (34.3)	0.02
Bronchoalveolar lavage	2/41 (4.8)	5/21 (23.8)	0.02
Death from all causes at 28 days, *n* (%)	7/58 (12)	37/85 (43.5)	< 0.05
Quantitative tracheal aspirate	2/17 (11.6)	29/64 (45.3)	0.01
Bronchoalveolar lavage	5/41 (12.1)	8/21 (38)	0.01
Intensive care unit duration of stay, days (SD)	17.2 (1.2)	22.7 (6.3)	< 0.05
Quantitative tracheal aspirate	17.2 (1.6)	22.4 (6.4)	< 0.05
Bronchoalveolar lavage	17.2 (1.1)	23.2 (6)	< 0.05
Hospital duration of stay, days (SD)	23.7 (2.8)	29.8 (11.16)	< 0.05
Quantitative tracheal aspirate	23.1 (4.4)	29.9 (11.16)	< 0.05
Bronchoalveolar lavage	23.8 (2.4)	29.8 (11.4)	0.02

Table 5 Pathogens and antibiotic agents associated with de-escalation of antibiotic therapy, in a prospective cohort of 143 patients with ventilator-associated pneumonia

Pathogens associated with de-escalation therapy	Antibiotics de-escalated Initial	Final	Patients in whom treatment was de-escalated, *n*
Quantitative tracheal aspirate			
MSSA – *Serratia marscecens*	L – M – A	PT	3
MSSA – *Serratia marscecens*	L – M – Q	PT	2
MSSA – *P. aeruginosa*	L – PT – A	CTZ – A	2
MRSA – *P. aeruginosa*	L – PT – Q	L – CTZ – Q	7
Streptococcus – P. aeruginosa	L – M – Q	CTZ – Q	3
Bronchoalveolar lavage			
MSSA – *P. aeruginosa*	L – M – A	PT – A	5
MRSA* – *P. aeruginosa*	L – M – A	L – PT – A	2
MRSA* – *P. aeruginosa*	L – PT – A	L – CTZ – A	2
Escherichia coli – Proteus	M – Q	PT	5
Klebsiella – Morganella morganii	M – Q	PT	4
Klebsiella	M – A	M	6
P. aeruginosa	M – A	CTZ – A	2
Streptococcus – P. aeruginosa	L – PT – Q	CTZ – Q	6
Haemophilus influenzae	PT – Q	Q	9

MSSA, methicillin-sensitive *Staphyloccoccus aureus*; *MRSA*, methicillin-resistant *Staphylococcus aureus*; *L*, linezolide; *M*, meropenem; *A*, amikacin; *Q*, quinolone; *PT*, piperacillin/tazobactam; *CTZ*, ceftazidime; *These *MRSA* were not taken into account in the pathogens associated with de-escalation of therapy, for only the antibiotic against *P. aeruginosa* was de-escalated and therefore the only pathogen associated with de-escalation of therapy was *P. aeruginosa*

Table 6 Pathogens and antibiotic agents not associated with de-escalation of antibiotic therapy, in a prospective cohort of 143 patients with ventilator-associated pneumonia

Pathogens not associated with de-escalation therapy	Antibiotics not de-escalated Initial	Final	Patients in whom treatment was not de-escalated, *n*
Bronchoalveolar lavage			
P. aeruginosa	PT – Q	PT – Q	10
P. aeruginosa	M – Q	M – Q	11
Quantitative tracheal aspirate			
MRSA – *P. aeruginosa*	L – PT – A	L – PT – A	11
MRSA – MSSA – *P. aeruginosa*	L – M – A	L – M – A	3
Klebsiella – Morganella	M – A	M – A	5
P. aeruginosa – Streptococcus	L – M – Q	L – M – Q	5
Serratia – Proteus	M – Q	M – Q	4
MRSA – *P. aeruginosa – Serratia*	L – PT – A	L – PT – A	1
Haemophilus – E. coli	M – Q	M – Q	9
MRSA – *P. aeruginosa*	L – PT – A	L – PT – A	4
MRSA – *P. aeruginosa – Proteus*	L – M – A	L – M – A	1
MRSA – MSSA	PT – A	PT – A	1
MRSA	L	L	5
Klebsiella – Haemophilus	L	L	2
Klebsiella	M – Q	M – Q	5
Serratia	M – Q	M – Q	6
Enterococcus	L	L	2

MSSA, methicillin-sensitive *Staphyloccoccus aureus*; *MRSA*, methicillin-resistant *Staphylococcus aureus*; *L*, linezolide; *M*, meropenem; *A*, amikacin; *Q*, quinolone; *PT*, piperacillin/tazobactam; *CTZ*, ceftazidime

of stay in ICU and in hospital were noted between patients in whom de-escalation of therapy was achieved by BAL and those in whom it was achieved by quantitative tracheal aspirate (Table 4).

De-escalation of antibiotic therapy by quantitative tracheal aspirate (Table 5) comprised: reduction in spectrum in 41.1% (7 of 17 patients), for *P. aeruginosa*; fewer drugs coupled with reduction in spectrum in 58.9% (10 of 17 patients). The combined drug number and spectrum reduction was due to cessation of the antistaphylococcal agent, coupled with spectrum reduction for *P. aeruginosa*, in five patients and with cessation of combination therapy and spectrum reduction, for *Serratia marcescens* that was identified instead of *P. aeruginosa*, in the rest.

De-escalation of antibiotic therapy by BAL (Table 5) comprised: reduction in spectrum in 14.6% (6 of 41 patients) for *P. aeruginosa*; fewer drugs in 14.6% (6 of 41 patients) as combination therapy was replaced by monotherapy for *Klebsiella* that was identified instead of *P. aeruginosa;* fewer drugs coupled with reduction in spectrum in 70.8% (29 of 41 patients). The combined drug number and spectrum reduction was due to cessation of the antistaphylococcal agent coupled with spectrum reduction for *P. aeruginosa* in 11 patients. In the rest, it was due to cessation of combination therapy for the anticipated *P. aeruginosa* that was not recovered coupled with spectrum reduction for the pathogens identified.

De-escalation of therapy by tracheal aspirate was not accomplished (Table 6) when there were not narrower spectrum agents available for the recovered, as anticipated, pathogens: MRSA and *P. aeruginosa* in 31.2% (20 of 64), MRSA alone in 10.9% (7 of 64), *Streptococcus* or *Enterococcus* in 10.9% (7 of 64) that was sensitive to oxazolidinone only, *P. aeruginosa* with *Proteus* in 1.6% (1 of 64) and other than *P. aeruginosa* Gram-negative bacteria in 45.4% (29 of 64). In these latter cases two species were cultured, of which one was sensitive only to meropenem and the other only to quinolone or aminoglycoside, preventing de-escalation of the initial combination regimen.

De-escalation of therapy by BAL was not accomplished (Table 6) when there were no narrower-spectrum agents available for the recovered, as anticipated, *P. aeruginosa*.

Discussion

In this study, we observed that 15-day and 28-day mortality could be further decreased by de-escalation of antibiotic therapy for patients with VAP who were appropriately treated and had favorable clinical response. Improvement in ICU and hospital duration of stay was also established for patients who get de-escalation therapy.

To the best of our knowledge, only a few studies have evaluated the effect of de-escalation therapy on outcomes in patients with VAP [4–8] and all have used clinical diagnosis, supported, when available, by cultures of quantitative tracheal aspirate or BAL, with the inherent risk for overestimation of the incidence of infection [9, 10, 20].

Recently, Kollef et al. found reduced mortality for patients who received de-escalation therapy compared to those who did not (17% vs. 23.7%) [6]. Improved mortality was also observed by Rello et al. with de-escalation of antibiotic therapy (18.4% vs. 43.4%) [7] and by Soo Hoo et al (8% vs. 23%) [8]. The diagnosis of VAP by two positive quantitative cultures, one tracheal aspirate and one BAL sample, in all study patients in our data, should probably be considered for the interpretation of the difference between our observations and those of Ibrahim et al. and of Micek et al., who found no benefits in mortality and duration of stay from de-escalation therapy [4, 5].

At least two factors may explain why patients in whom treatment was de-escalated had significantly reduced 15-day and 28-day mortality, compared with patients in whom it was not, despite the absence of significant differences in admission and baseline characteristics, predicted mortality, prescribed antibiotics and identified pathogens for the two groups. First, patients in whom antibiotic therapy was de-escalated ended up receiving fewer antibiotics. Stopping unnecessary antibiotics helps to prevent potentially harmful side effects and has been shown to reduce airway colonization [21–23] and the risk of secondary episodes of infection [4, 23], which are known to adversely affect patient outcome [21, 24]. Within this context should probably be interpreted the good outcomes that we observed, in consistency with previous reports [21], for patients assigned to management by BAL, as more than half of them had de-escalation of antibiotic therapy and therefore ended up receiving fewer unnecessary antibiotics.

Second, patients in whom antibiotic therapy was de-escalated had shorter exposure to acute-care settings, as they had shorter duration of ICU and hospital stay. Contact with such settings [12] has been suggested to be among the factors that are likely to influence the potential for resistance of pathogens identified in VAP [13, 25, 26]. Reducing duration of exposure to an acute-care setting may help to decrease exposure to several procedures and therapies that are known to modify host defenses [27, 28], in the midst of a steady selection pressure for multi-resistant microorganisms [29], which are well known to adversely affect patient outcome [30, 31].

Our study was limited by its performance within a single ICU and the relatively large subset of patients that was excluded, namely those in whom de-escalation therapy was not according to the protocol and those in whom the first available service for respiratory sample collection was not used. In addition, the diagnosis of VAP and the appropriateness of the empiric treatment had to be confirmed by both quantitative tracheal aspirate and BAL. Thus, the results of this study cannot necessarily be extended to other populations. Another limitation is that investigators were aware of the patients' assignment and of their de-escalation therapy status. However, obstacles in blinding were posed by the necessity to collect both samples in all study patients and to modify treatment in the context of de-escalation therapy. Nevertheless, our efforts were focused on standardizing care and using rigorous criteria to evaluate outcomes. Finally, it is important to acknowledge that our study was not specifically designed to test the hypothesis that de-escalation therapy is superior to a non-de-escalation regimen in terms of improving clinical outcomes. Only a prospective randomized trial comparing these two approaches would be able to answer such a question.

In summary, for patients with VAP who were appropriately treated and had favorable clinical response, we found that mortality and duration of ICU and hospital stay could be further reduced by de-escalation therapy. This finding provides arguments for stopping overuse of antibiotics when alternative regimens, with narrower-spectrum or fewer antibiotics, are available.

References

1. Chastre J (2005) Conference summary: ventilator associated pneumonia. Respir Care 50:975–983
2. Niedermann MS (2006) The importance of de-escalating antimicrobial therapy in patients with ventilator-associated pneumonia. Semin Respir Crit Care Med 27:45–50
3. Chastre J (2005) Antibiotic prescribing for ventilator-associated pneumonia: get it right from the beginning but be able to rapidly deescalate. Intensive Care Med 31:1465–1465 DOI 10.1007/s00134–005-2696-z
4. Ibrahim EH, Ward S, Sherman G, Scaiff R, Fraser VJ, Kollef MH (2001) Experience with a clinical guideline for the treatment of ventilator-associated penumonia. Crit Care Med 29:1109–1115
5. Micek ST, Ward S, Fraser VJ, Kollef MH (2004) A randomized controlled trial of an antibiotic discontinuation policy for clinically suspected ventilator-associated pneumonia. Chest 125:1791–1799
6. Kollef MH, Morrow LE, Niedermann MS, Leeper KV, Anzueto A, Benz-Scott L, Rodino JF (2006) Clinical characteristics and treatment patterns among patients with ventilator-associated pneumonia. Chest 129(5):1210–1218
7. Rello J, Vidaur L, Sandiumenge A, Rodriguez A, Gualis B, Carmen B, Diaz E (2004) De-escalation therapy in ventilator-associated pneumonia. Crit Care Med 32:2183–2190 DOI 10.1097/01.CCM.0000145997.10438
8. Soo Hoo GW, Wen E, Nguyen TV, Goetz MD (2005) Impact of clinical guidelines in the management of severe hospital acquired pneumonia. Chest 128:2778–2787

9. Luyt CE, Chastre J, Fagon JY (2004) Value of the clinical pulmonary infection score for the identification and management of ventilator-associated pneumonia. Intensive Care Med 30:844–852 DOI 10.1007/s00134-003-2125-0
10. Schurink CA, Van Nieuwenhoven CA, Jacobs JA, Rozenberg-Arska M, Joore HC, Buskens E, Hoepelman AI, Bonten MJ (2004) Clinical pulmonary infection score for ventilator-associated pneumonia: accuracy and inter-observer variability. Intensive Care Med 30:217–224
11. Chastre J, Wolff M, Fagon JY, Chevret S, Thomas F, Wermert D, Clementi E, Gonzalez J, Jusserand D, Asfar P, Perrin D, Fieux F, Aubas S (2003) Comparison of 8 vs. 15 days of antibiotic therapy for ventilator-associated pneumonia in adults. JAMA 290(19):2588–2598
12. American Thoracic Society Documents (2005) Guidelines for the management of adults with hospital–acquired, ventilator-associated and healthcare-associated pneumonia. Am J Respir Crit Care Med 172:388–416
13. Trouillet JL, Chastre J, Vuagnat A, Joly-Guillou ML, Combaux D, Dombret D, Dombret MC, Gibert C (1998) Ventilator-associated pneumonia caused by potentially drug-resistant bacteria. Am J Respir Crit Care Med 1157:531–539
14. Niedermann MS (2006) De-escalation therapy in ventilator-associated pneumonia. Curr Opin Crit Care Med 12:452–457
15. Lisboa T, Rello J (2006) De-escalation in lower respiratory tract infections. Curr Opin Pulm Med 12:364–368
16. Kollef MH, Niedermann MS, Leeper KV (2004) Escalation/de-escalation of initial empiric ventilator-associated pneumonia therapy: interim results from the assessment of local antibiotic resistance measures study. Chest 126:718
17. Le Gall JR, Lemeshow S, Saulnier F (1993) A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. JAMA 270:2957–2963
18. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonca A, Bruining H, Reinhart CK, Suter PM, Thijs LG (1996) The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the working group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med 22:707–710
19. Andrews P, Azoulay E, Antonelli M, Brochard L, Brun-Buisson C, Dobb G, Fagon JY, Gerlach H, Groeneveld J, Mancebo J, Metnitz P, Nava S, Pugin J, Pinsky M, Radermacher P, Richard C, Tasker R (2006) Year in review in Intensive Care Medicine, 2005. II. Infection and sepsis, ventilator-associated pneumonia, ethics, haematology and haemostasis, ICU organization and scoring, brain injury. Intensive Care Med 32:380–390 DOI 10.1007/s00134-005-0060-y
20. Fagon JY (2006) Diagnosis and treatment of ventilator-associated pneumonia: Fiberoptic bronchoscopy with bronchoalveolar lavage is essential. Semin Respir Crit Care Med 27(1):34–44
21. Fagon JY, Chastre J, Wolff M, Gervais C, Parer-Aubas S, Stephan F, Similowski T, Mercat A, Diehl JL, Sollet JP, Tenaillon A (2000) Invasive and noninvasive strategies for management of suspected ventilator-associated pneumonia. Ann Intern Med 132:621–630
22. Denesen PJ, van de Ven AJ, Kessels AG, Ramsay G, Bonten MJ (2001) Resolution of infectious parameters after antimicrobial therapy in patients with ventilator-associated pneumonia. Am J Respir Crit Care Med 163(6):1371–1375
23. Singh N, Rogers P, Atwood CW, Wagener MM, Yu VL (2000) Short course empiric antibiotic therapy for pulmonary infiltrates in the intensive care unit: a proposed solution for indiscriminate antibiotic prescription. Am J Respir Crit Care Med 162:505–511
24. Niedermann MS (2004) Therapy of ventilator-associated pneumonia: what more can we do to use less antibiotics? Crit Care Med 32:2344–2345
25. Giantsou E, Liratzopoulos N, Efraimidou E, Panopoulou M, Alepopoulou E, Kartali-Ktenidou S, Minopoulos G, Zakynthinos S, Manolas KI (2005) Both early-onset and late-onset ventilator-associated pneumonia are mainly caused by potentially multiresistant bacteria. Intensive Care Med 31:1388–1394 DOI 10.1007/s00134-005-2697-y
26. Ibrahim EH, Ward S, Sherman G, Kollef M (2000) A comparative analysis patients with early vs. late onset nosocomial pneumonia in ICU setting. Chest 117:1434–1442
27. Valles J, Marischal D, Cortes P, Coll P, Villagra A, Diaz E, Artigas A, Rello J (2004) Patterns of colonization by *Pseudomonas aeruginosa* in intubated patients: a 3-year prospective study of 1,607 isolates using pulsed-field gel electrophoresis with implications for prevention of ventilator-associated pneumonia. Intensive Care Med 30:1768–1775
28. Isakow W, Kolle MH (2006) Preventing ventilator-associated pneumonia: an evidence-based approach of modifiable risk factors. Semin Respir Crit Care Med 27:5–17
29. Prince AS (2002) Biofilms, antimicrobial resistance and airway infection. N Engl J Med 347:847–857
30. Chastre J, Fagon JY (2002) Ventilator-associated pneumonia. Am J Respir Crit Care Med 165:867–903
31. Hoffken G, Niedermann MS (2002) The importance of a de-escalating strategy for antibiotic treatment of pneumonia in the ICU. Chest 122:2183–2196