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

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 empirical 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 mm³, ratio of partial pressure of arterial oxygen to fraction of inspired oxygen (PaO₂/FiO₂), 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 asthmatic                        | 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 |
| PaO2/FiO2, 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; PaO2/FiO2, 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

| Antibiotic | De-escalation therapy (n = 58) | No de-escalation therapy (n = 85) | p-value |
|------------|-------------------------------|----------------------------------|---------|
| 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 |
| 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

| 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 marcescens*                 | L – M – A                       | PT   | 3                                           |
| MSSA – *P. aeruginosa*                       | L – M – Q                       | PT   | 2                                           |
| MSSA – *P. aeruginosa*                       | L – PT – A                      | CTZ – A | 2                                    |
| MSSA – *P. aeruginosa*                       | L – PT – Q                      | L – CTZ – Q | 7                                    |
| MSSA – *P. aeruginosa*                       | L – M – Q                       | CTZ – Q | 3                                           |
| Bronchoalveolar lavage                       |                                 |      |                                             |
| MSSA – *P. aeruginosa*                       | L – M – A                       | PT – A | 5                                           |
| M RSA* – *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 *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*; L, linezolid; M, meropenem; A, amikacin; Q, quinolone; PT, piperacillin/tazobactam; CTZ, cefazidime; *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 | Patients in whom treatment was not de-escalated, n |
|-----------------------------------------------------|-------------------------------|-----------------------------------------------|
| P. aeruginosa                                        | PT–Q                          | P. aeruginosa                                  | 10                                      |
| MRSA – P. aeruginosa                                | L – PT – A                     | MRSA – P. aeruginosa                           | 11                                      |
| MRSA – MSSA – P. aeruginosa                         | L – M – A                      | MRSA – MSSA                                    | 3                                       |
| Klebsiella – Morganella                             | M – A                          | Klebsiella – Morganella                        | 5                                       |
| P. aeruginosa – Streptococcus                       | L – M – Q                      | P. aeruginosa – Streptococcus                  | 5                                       |
| Serratia – Proteus                                  | M – Q                          | Serratia – Proteus                             | 4                                       |
| MRSA – P. aeruginosa                                | L – PT – A                      | MRSA – P. aeruginosa                           | 1                                       |
| Haemophilus – E. coli                               | M – Q                          | Haemophilus – E. coli                          | 9                                       |
| MRSA – P. aeruginosa                                | L – PT – A                      | MRSA – P. aeruginosa                           | 1                                       |
| MRSA – MSSA                                         | PT – A                          | MRSA – MSSA                                    | 1                                       |
| MRSA                                                | L                              | MRSA                                          | 5                                       |
| Klebsiella – Haemophilus                            | L                              | Klebsiella – Haemophilus                      | 2                                       |
| Klebsiella                                          | M – Q                          | Klebsiella – Haemophilus                      | 5                                       |
| Serratia                                            | M – Q                          | Serratia – Proteus                             | 6                                       |
| Enterococcus                                        | L                              | Enterococcus                                   | 2                                       |

MSSA, methicillin-sensitive Staphylococcus 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.
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