Saad Nseir[1,2], Ignacio Martin-Loeches[3]

Ventilator-associated tracheobronchitis: where are we now?

Traqueobronquite associada ao ventilador: onde nos encontramos?

1. Critical Care Department, R. Salengro Hospital, University Hospital of Lille - Lille, France.
2. University of Lille Nord de France - Lille, France.
3. Multidisciplinary Intensive Care Research Organization (MICRO), St James's University Hospital, Trinity Centre for Health Sciences - Dublin, Ireland.

Ventilator-associated tracheobronchitis (VAT) is a common intensive care unit (ICU)-acquired infection. Its incidence ranges from 1.4 to 19% of critically ill patients receiving invasive mechanical ventilation.[1-4] This infection is considered as an intermediate process between colonization and ventilator-associated pneumonia (VAP).[5] Histological studies revealed a continuum between these two infections. Several definitions are available for VAT. However, all of these definitions have some limitations. The most accepted and frequently used definition include the following criteria: fever >38º C with no other cause, purulent tracheal secretions, positive tracheal aspirate ($\geq 10^5$cfu/mL), and absence of new infiltrate on chest X-ray.[2] VAT is frequently caused by *Gram*-negative bacilli. *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Acinetobacter baumannii* are the most common pathogens isolated from respiratory secretions of VAT patients.[6]

Previous studies have reported a prolonged duration of mechanical ventilation and a prolonged ICU stay in VAT patients.[4,7] This negative impact on patient outcome is related to increased inflammation of the lower respiratory tract and sputum production. Extubation failure has been noted, and difficult weaning could result from increased sputum production. In addition, higher rates of VAP were reported in patients with VAT compared with those without VAT. In a recent multicenter observational study conducted in 122 VAT patients,[8] the incidence of VAP was two-fold higher in patients with VAT compared with those without VAT (13.9% versus 7%). Although the mortality attributed to VAP remains a matter for debate, VAP is associated with a longer duration of mechanical ventilation, longer length of ICU stay, and increased hospital cost.[9]

A recent international survey was conducted to determine the current practices in the clinical and microbiological diagnosis of VAT and to evaluate perceptions of the impact of VAT on patient outcomes.[10] A total of 288 ICUs from 16 different countries answered the survey, including 147 (51%) from Latin America and 141 (49%) from Spain, Portugal, and France. The majority of respondents (n=228; 79.2%) reported making the diagnosis of VAT based on clinical and microbiological criteria, and 40 (13.9%) reported making the diagnosis based on clinical criteria alone. Approximately half (50.3%) of the respondents agreed that patients should receive antibiotics for the treatment of VAT. Out of all respondents, 269 (93.4%) assumed that a VAT episode increases the ICU length of stay. Half of the physicians felt that VAT increases the risk of mortality.

Two recent randomized studies evaluated the impact of antimicrobial treatment on the outcome of VAT patients.[11,12] The first was a randomized

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Corresponding author:
Saad Nseir
Centre de Réanimation, Hôpital R. Salengro
Rue Emile Laine, CHRU de Lille
59037 Lille Cedex, France
E-mail: s-nseir@chru-lille.fr

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placebo-controlled blinded trial that aimed to determine the impact of aerosolized antibiotics on the outcomes in patients with VAT.[11] Forty-three patients were randomized to receive aerosolized antibiotics or placebo for 14 days. The choice of aerosolized antibiotic was based on *Gram* stain. Vancomycin and gentamycin were used in patients with *Gram*-positive and *Gram*-negative microorganisms, respectively. Both antibiotics were used if both *Gram*-positive and *Gram*-negative microorganisms were present. Most of the 43 included patients were treated with systemic antibiotics because of concomitant VAP. The authors found that the use of aerosolized antibiotics was associated with significantly lower rates of VAP at the end of treatment (35.7% versus 78.6%, p=0.007), reduced subsequent usage of systemic antibiotics (42% versus 70%, p=0.042), a higher number of days free of mechanical ventilation (median 10 versus 0, p=0.069) and an increased percentage of survivors with successful weaning (80% versus 45%, p=0.046). Interestingly, lower rates of antimicrobial resistance were also found in patients treated with aerosolized antibiotics compared with those who received placebo (0%, versus 16.6%, p=0.005). However, there was no significant impact on mortality (21.1% versus 16.7%, p=0.9). The limitations of this study included lack of specificity in the definition of VAT, the small number of included patients, coexistence of VAP, and use of systemic antibiotics in most patients.

The impact of systemic antimicrobial treatment on outcome in VAT patients was evaluated in a multicenter, randomized, unblinded, controlled study.[12] In all patients, quantitative tracheal aspirate was performed at ICU admission and weekly. Systemic antibiotics were given for 8 days based on the results of previous endotracheal aspirate. The study was terminated early because a planned interim analysis revealed a significant difference in the mortality rate between the two groups. A total of 58 patients were included (22 patients in the antibiotic group and 36 patients in the control group). The duration of mechanical ventilation (29±17 versus 26±15 days, p=0.816) and ICU stay (40±23 versus 36±21 days, p=0.816) were similar in the two groups. However, number of days free of mechanical ventilation was significantly higher in the antibiotic group compared with the control group (median [IR] of 12 [8-24] versus 2 [0-6], p<0.001). In addition, subsequent VAP (13% versus 47%, p=0.011) and ICU mortality rates (18% versus 47%, p=0.011) were significantly lower in the antibiotic group compared with the control group. The lower ICU mortality in the antibiotic group is likely to be related to the higher rate of VAP in control patients. Another potential explanation might be the difficulty in distinguishing VAT from early VAP because of the low specificity of portable chest radiography. The limitations of this study included the small number of included patients, absence of blinding, and lack of standardized antibiotic treatment.

A recent meta-analysis[13] included the two randomized trials discussed above,[11,12] eight studies evaluating various strategies for the prevention of VAT, and other observational studies. The authors found that administration of systemic antimicrobials (with or without aerosolized antimicrobials) in patients with VAT was not associated with decreased mortality when compared to placebo or no treatment (odds ratio - OR 0.56, 95% confidence interval - CI95% 0.27-1.14). However, most of the studies that provided relevant data noted that administration of antimicrobial agents, as opposed to placebo or no treatment, in patients with VAT was associated with a lower frequency of subsequent pneumonia and more ventilator-free days; however, the length of ICU stay and duration of mechanical ventilation were not shortened. In addition, selective digestive decontamination (SDD) was not shown to be an effective preventive strategy against VAT (OR 0.62, 95%CI 0.27-1.14).

In the recent observational multicenter study discussed above, 74 (60%) patients received antimicrobial treatment, including 58 (47.5%) patients who received appropriate antimicrobial treatment.[8] Appropriate antibiotic treatment was the only factor independently associated with reduced risk for transition from VAT to VAP (OR [95% CI]: 0.12 [0.02-0.59], p=0.009). The numbers of VAT patients needed to treat to prevent one episode of VAP or one episode of VAP related to *P. aeruginosa* were 5 and 34, respectively.

Antibiotic treatment is a well-known risk factor for colonization and infection related to multidrug-resistant bacteria. A recent international study on nosocomial bacteremia performed in 1156 patients found that multidrug-resistant bacteria were independently associated with mortality (OR [95%CI] 1.49 [1.07-2.06]).[14]

The results of the TAVeM international study should be helpful for validating an accepted definition of VAT.[15] In fact, more than 3000 patients requiring invasive mechanical ventilation for >48 hours were included. The first analyses should provide interesting data on the incidence of VAT and on its impact on outcome. Further randomized controlled studies should be performed to determine the impact of antimicrobial treatment on the outcomes of VAT patients.

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