ERJ Express. Published on February 8, 2018 as doi: 10.1183/13993003.01656-2017

EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Original article

Impact of immunosuppression on incidence, aetiology and outcome of ventilator-associated lower respiratory tract infections

Anne-Sophie Moreau, Ignacio Martin-Loeches, Pedro Povoa, Jorge Salluh, Alejandro Rodriguez, Arnaud W Thille, Emilio Diaz Santos, Elisa Vedes, Suzana Margareth Lobo, Bruno Mégarbane, Esperanza Molero Silvero, Luis Coelho, Laurent Argaud, Rafael Sanchez Iniesta, Julien Labreuche, Anahita Rouzé, Saad Nseir

Please cite this article as: Moreau A-S, Martin-Loeches I, Povoa P, *et al*. Impact of immunosuppression on incidence, aetiology and outcome of ventilator-associated lower respiratory tract infections. *Eur Respir J* 2018; in press (https://doi.org/10.1183/13993003.01656-2017).

Impact of immunosuppression on incidence, etiology and outcome of ventilator-associated lower respiratory tract infections

Anne-Sophie Moreau[1], Ignacio Martin-Loeches[2], Pedro Povoa[3,4], Jorge Salluh[5],

Alejandro Rodriguez[6], Arnaud W Thille[7], Emilio Diaz Santos[8], Elisa Vedes[9], Suzana Margareth Lobo[10], Bruno Mégarbane[11], Esperanza Molero Silvero[12], Luis Coelho[3,4], Laurent Argaud[13], Rafael Sanchez Iniesta[14], Julien Labreuche[15], Anahita Rouzé[1], Saad Nseir[1,16] for the TAVeM study Group

1- Centre de Réanimation, CHU Lille, F-59000 Lille, France

2- Department of Clinical Medicine, Trinity College, Welcome Trust-HRB Clinical Research Facility, St James Hospital, Dublin, Ireland.

3- Unidade de Cuidados Intensivos Polivalente, Hospital de São Francisco Xavier, Centro Hospitalar de Lisboa Ocidental, Lisboa, Portugal

4- NOVA Medical School, CEDOC, Universidade Nova de Lisboa, Lisboa, Portugal

5- Department of Critical Care, D'Or Institute for Research and Education, Rua Diniz Cordeiro, 30. Botafogo, Rio De Janeiro, 22281-100, Brazil

6- Critical Care Department, Joan XXIII University Hospital, Mallafre Guasch 4, 43007, Tarragona, Spain

7- CHU de Poitiers, Réanimation Médicale, Poitiers, France; INSERM, CIC-1402, équipe 5 ALIVE, Poitiers, France; Université de Poitiers, Faculté de Médecine et de Pharmacie de Poitiers, Poitiers, France.

8- Critical Care Center, Sabadell Hospital, Corporación Sanitaria Universitaria Parc Taulí, Universitat Autonoma de Barcelona, Sabadell, Spain; CIBER de Enfermedades Respiratorias (CIBERES), Spain

9- Unidade de Cuidados Intensivos do Hospital da Luz, Lisboa, Portugal

10- Faculdade de Medicina de São José do Rio Preto – Brazil

11- Department of Medical and Toxicological Critical Care, Lariboisière Hospital, Paris-Diderot University, INSERM UMRS-1144, Paris, France

12- Intensive Medicine Unit, Gómez Ulla Hospital, Madrid, Spain

13- Service de Réanimation Médicale, Hôpital Edouard Herriot, Hospices Civils de Lyon, Lyon, France.

14- General de Albacete - Spain

15-CHU Lille, Clinique de Santé Publique, plateforme d'aide méthodologique, 59037, Lille Cedex, France

16- Lille University, Medicine School, 59000-F Lille, France

Conflicts of interest:

SN: MSD, and Medtronic (lecture), CielMedical, and Bayer (advisory board); other authors none.

Funding: none

Corresponding author:

Pr. Saad Nseir, Centre de Réanimation - Hôpital Salengro, CHRU Lille, 59037 LILLE Cedex

Tel : 03.20.44.40.84, Email : s-nseir@chru-lille.fr

ABSTRACT

The aim of this planned analysis of the prospective multinational TAVeM database was to determine the incidence, etiology and impact on outcome of ventilator-associated lower respiratory tract infections (VA-LRTI) in immunocompromised patients.

All patients receiving mechanical ventilation for >48h were included. Immunocompromised patients (n= 663) were compared with non-immunocompromised patients (n=2297).

The incidence of VA-LRTI was significantly lower in immunocompromised than in non-immunocompromised patients (16.6% vs 24.2%, p<0.0001, Subhazard ratio 0.65 (0.53-0.80)). Similar results were found regarding ventilator-associated tracheobronchitis (VAT) (7.3% vs 11.6%, p=0.002, 0.61 (0.45-0.84)), and ventilator-associated pneumonia (VAP) (9.3% vs 12.7%, p=0.019, 0.72 (0.54-0.95)). Among patients with VA-LRTI, the rates of multidrug resistant (MDR) bacteria (72% vs 59%, p=0.011), and ICU mortality were significantly higher in immunocompromised compared with non-immunocompromised patients (54%, vs 30%, p<0.0001, OR 2.68 (95% CI 1.78-4.02)). In patients with VAP, mortality rates were higher in immunocompromised than in non-immunocompromised patients (64% vs 34%, p<0.001).

Incidence of VA-LRTI was significantly lower in immunocompromised compared with non-immunocompromised patients, but it was associated with significantly higher mortality rate. MDR pathogens were more frequently found in immunocompromised patients with VA-LRTI.

Keywords

Immunosuppression, lower respiratory tract infections, ventilator-associated, pneumonia, tracheobronchitis, intensive care unit.

Abbreviations

BAL, bronchoalveolar lavage; CFU, colony forming unit; ETA, endotracheal aspirate; ICU, intensive care unit; MDR, multidrug resistant bacteria; MSSA, methicillin-sensitive *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*; SAPS, simplified acute physiology score; SOFA, sequential organ failure assessment; VA-LRTI, ventilator-associated lower respiratory tract infection; VAP, ventilator-associated pneumonia; VAT, ventilator-associated tracheobronchitis

INTRODUCTION:

Ventilator-associated lower respiratory tract infections (VA-LRTI) are the most common infectious complication in the intensive care unit (ICU) [1, 2]. They include both ventilator-associated tracheobronchitis (VAT) and ventilator-associated pneumonia (VAP). VAT has been proposed as an intermediate stage between colonization of the lower respiratory tract and ventilator-associated pneumonia (VAP) [3, 4]. This infection is associated higher rates of subsequent VAP, and prolonged duration of mechanical ventilation [5–7]. Recently, our group have shown that VAT was a separate entity, responsible for increased duration of mechanical ventilation and ICU length of stay in a large cohort of medical and surgical patients [2]. VAT was not associated with increased mortality rates, but transition from VAT to VAP was a risk factor for mortality and appropriate antibiotic treatment was protective. Further, several previous studies demonstrated that VAP was associated with increased morbidity, mortality, and cost in critically ill patients [8–11]. However, the mortality attributable to VAP is still a matter for debate [10, 12].

Immunocompromised patients have a particularly poor outcome in the ICU, due to a higher risk of infection, especially to opportunistic pathogens, higher severity of illness, immunosuppression itself, and poor performance status [13, 14]. They often receive large-spectrum antibiotic treatment, thus increasing the risk for developing multidrug resistant bacteria (MDR) [15]. The main cause for admission of these patients to the ICU is acute respiratory failure [16]. Although their outcomes have substantially improved in recent years, the prognosis remains poor with hospital mortality rates rising up to 60% in mechanically ventilated patients [17]. However, to our knowledge, no study to date has specifically evaluated VA-LRTI in this population. We hypothesized that immunocompromised patients would develop more VA-LRTI than non-immunocompromised patients, given the context or altered host defenses. Therefore, we conducted this study to determine the incidence, etiology and outcome of these infections in immunocompromised patients, and to compare them with patients with no apparent immunosuppression.

MATERIAL AND METHODS:

Patients

This study is a planned analysis of the large multinational TAVeM database, which prospectively followed patients older than 18 years admitted to 114 ICUs in Europe and Latin America, and receiving mechanical ventilation for more than 48 hours between Sept 1, 2013 and July 31, 2014 [2].

Participating centers either received ethics approval from their institutions or ethics approval was waived (institutional review board number 2013515). Informed consent was waived because of the observational nature of the study.

Immunocompromised patients were those with ongoing neoplasia, hematological malignancy, acquired immune deficiency syndrome (AIDS), allogeneic stem cell transplant, immunosuppressive drugs, or organ transplant [18].

Procedures and definitions

Patients were prospectively followed up for outcome until death or ICU discharge. Demographical data were obtained along with clinical data including comorbidities, prognostic scores, antibiotic use, and diagnostic procedures for VAP and VAT.

Shortly, the diagnosis of VA-LRTI was based on the presence of at least two of the following criteria: body temperature of more than 38·5°C or less than 36·5°C, leucocyte count greater than 12 000 cells per µL or less than 4000 cells per µL, and purulent endotracheal aspirate (ETA). Additionally, all episodes of infection had to have a positive microbiological isolation in the ETA of at least 10^5 colony-forming units (CFU) per mL, or with bronchoalveolar lavage (BAL) of at least 10^4 CFU per mL, to be included in the final analysis.

VAT was defined with the aforementioned criteria with no radiographical signs of new infiltrate; VAP was

defined by the presence of new or progressive infiltrate on chest radiograph. VAP was deemed as occurring subsequently to VAT if it was diagnosed in the 96 h period after diagnosis of tracheobronchitis, and the same microorganism caused both infections. VAP was considered as early-onset when it was diagnosed <5d, and late-onset when it was diagnosed ≥5d, after starting mechanical ventilation [19].

Empirical antibiotic therapy was defined as that given before microbiological documentation of infection. Antibiotic treatment was considered appropriate when at least one antibiotic, active *in vitro* on all organisms causing VA-LRTI, was administrated to treat these infections [20]. Microbiological identification and susceptibility tests were performed using standard methods. MDR was defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories [21]. More details on methods are available in the TAVeM principal paper [2].

Outcomes

The primary aim of our study was to determine the incidence of VA-LRTI, including VAT and VAP, comparing immunocompromised patients and non-immunocompromised patients. Our secondary objectives were to determine etiology and impact on outcome (length of stay in the ICU and hospital, days with mechanical ventilation and mortality) of VA-LRTI in immunocompromised patients, as compared to non-immunocompromised patients. We also studied the effect of appropriate antibiotic treatment on progression from VAT to VAP in immunocompromised patients as compared to non-immunocompromised patients.

Statistical analysis:

We used SPSS software (SPSS Inc, IBM, New York, NY, version 22) for data analysis. The incidence, etiology and outcome of VA-LRTI were compared between immunocompromised and non-immunocompromised patients. Only first episodes of VAT and VAP were taken into account.

Categorical variables were described as numbers and frequencies (%), normally distributed continuous variables as means (standard deviation (SD)), and skewed continuous variables as medians (interquartile range (IQR)). We used χ^2 tests or Fischer's exact test to compare qualitative variables, and Student's t tests or Mann-Whitney U and non-parametric Kruskal-Wallis tests to compare normally distributed and skewed continuous variables, as appropriate. All p values were two-tailed. Differences were considered as significant if p was less than 0.05.

Cumulative incidence of VA-LRTI was estimated using extubation and death as competing risks, based on the approach of Kalbfleisch and Prentice [22]. Comparison of cumulative incidence of VA-LRTI between immunocompromised and non-immunocompromised patients was performed using Fine-Gray model [23]. Subhazard ratios (SHRs) were derived from these models, as effect size and proportional subhazards assumption were assessed by examining the Schoenfeld residuals.

Univariate and multivariate analyses were used to determine factors associated with ICU-mortality in patients with VA-LRTI. All variables with p value<0.1 by univariate analysis were included in a Cox proportional hazards regression model using a stepwise backward elimination and based on a binary outcome of being discharged from the ICU dead or alive. For each candidate factor, proportional hazards were assessed by examining the Schoenfeld residuals. Effect sizes were expressed as hazard ratios.

RESULTS:

Patient characteristics

Among the 2960 included patients, 663 (22%) had a known immunosuppression, mainly nonmetastatic solid cancer, and immunosuppressive drug use (Table 1, Figure 1). Age, simplified acute physiology score (SAPS) II, sequential organ failure assessment (SOFA) score, percentage of patients with chronic kidney disease, and medical category of admission were significantly higher in immunocompromised patients, compared with non-immunocompromised patients. Percentage of patients with alcohol abuse history was significantly lower in immunocompromised patients compared with non-immunocompromised patients. No significant difference was found between the two groups for other patient characteristics (Table 2). Reasons for ICU admission are summarized in online supplementary material.

Among patients with VA-LRTI, the rate of prior antibiotic treatment was significantly higher in immunocompromised patients compared with non-immunocompromised patients (87 of 111 (78%) versus 355 of 540 (66%), *p*=0.009, OR (95% CI) 1.89 (1.16-3.1)). Similar results were found in the subgroups of patients with VAT (41/52 [79%] versus 169/263 [64%], in immunocompromised and non-immunocompromised patients, respectively, *p*=0.041), but not in those with VAP (46/59 [78%] versus 186/277 [67%], in immunocompromised and non-immunocompromised patients, respectively, *p*=0.1).

Incidence of VA-LRTI

The incidence of VA-LRTI was significantly lower in immunocompromised patients as compared to non-immunocompromised patients. Similarly, the incidence of VAT or VAP was significantly lower in immunocompromised patients as compared to non-immunocompromised patients (Table 3). The rate of patients with early onset VA-LRTI [19] was not significantly different between patients with immunosuppression and those with no immunosuppression (36 of 116 (31%) vs 229 of 568 (40%), p = 0.33). Similar results were found in the subgroups of patients with VAT (16 of 52 (31%) vs 101 of 267 (38%), p =

0.32), or with VAP (20 of 64 (31%) vs 128 of 302 (42%), p = 0.099).

Multidrug resistant bacteria

In patients with VA-LRTI, the rate of MDR bacteria was significantly higher in immunocompromised patients compared to non-immunocompromised patients (83 of 116 (72%) vs 338 of 573 (59%) patients, p = 0.011, OR (95% CI) 1.75 (1.13-2.71). Similar results were found in the subgroup of patients with VAP (49 of 64 (78%) vs 176 of 305 (58%) patients, p = 0.005, OR (95% CI) 2.39 (1.29-4.48), but not in VAT patients (34 of 52 (65%) vs 162 of 268 (60%) patients, p = 0.52).

Among patients with VA-LRTI, although methicillin-resistant *Staphylococcus aureus* (MRSA), and *Enterobacter* spp. were significantly more frequent in immunocompromised patients as compared with non-immunocompromised patients; methicillin-sensitive *Staphylococcus aureus* (MSSA) was significantly less frequent in immunocompromised patients as compared with non-immunocompromised patients. No significant difference was found in the incidence of other bacteria between immunocompromised and non-immunocompromised patients.

Progression from VAT to VAP

The incidence of progression from VAT to VAP was not significantly different in immunocompromised and non-immunocompromised patients (7/52 (13%) versus 32/268 (12%), *p*=0.69). The percentage of patients who received appropriate antibiotic treatment for VA-LRTI was not significantly different between immunocompromised and non-immunocompromised patients (77% versus 79%, *p*=0.5). Similar results were obtained in VAT and VAP subgroups (data not shown). Among immunocompromised patients with VAT, 39/52 (75%) received appropriate antibiotics. The percentage of immunocompromised patients with progression from VAT to VAP was significantly lower in patients who received appropriate than in those who received inappropriate antibiotic treatment (3/39 (8%) versus 4/13 (31%), *p*=0.035, OR 0.19 (95% CI 0.035-0.992)).

Impact of immunosuppression on VA-LRTI outcomes

Among patients with VA-LRTI, ICU mortality rate was higher in immunocompromised patients as compared to non-immunocompromised patients (54% versus 30%, p <0.0001, OR 2.68 (95% CI 1.78-4.02)). Mortality was significantly higher in case of VAP in both groups, as compared to patients with no VA-LRTI and patients with VAT (Table 4). In VAP patients, ICU mortality was significantly higher in immunocompromised compared with non-immunocompromised patients. Furthermore, in both groups, VA-LRTI were associated with longer duration of mechanical ventilation and ICU length of stay (Table 4).

Immunosuppression was independently associated with ICU-mortality in patients with VA-LRTI (Table 5).

Additional results are provided in the online supplementary material.

DISCUSSION

Our results show that the incidence of VA-LRTI was significantly lower in immunocompromised patients compared with non-immunocompromised patients. Additionally, immunocompromised patients received more frequently previous antibiotic treatment and developed more frequently VAP related to MDR bacteria, as compared with non-immunocompromised patients. The development of VAT or VAP in this population was associated with increased duration of mechanical ventilation, and VAP was associated with significantly increased ICU mortality, compared with non-immunocompromised patients.

To our knowledge, this is the first study on VA-LRTI in this population. The TAVeM study is the largest prospective multicenter international and observational study of the natural history and incidence of VA-LRTI, and it generated robust and reproducible results [2].

The lower incidence of VA-LRTI, including VAT and VAP, in immunocompromised patients is rather surprising, as we expected that immunocompromised patients would develop more VA-LRTI than non-immunocompromised patients, given the context of immunosuppression. One could argue that we underdiagnosed these infections because of neutropenia, but only nine patients had neutropenia in our large cohort. Further, diagnostic criteria used in our study were strict, and detailed microbiology was required.

The lower incidence of VA-LRTI is probably linked to a higher exposure to previous antibiotic treatment in immunocompromised patients, and as a consequence, the higher rate of MDR-related VA-LRTI in this population. Previous randomized controlled, and observational studies suggested that antibiotic treatment in mechanically ventilated patients with coma was associated with significantly reduced incidence of early-onset VAP [24–26]. However, antibiotic treatment is a well-known risk factor for late-onset VAP related to MDR [27–29]. Previous studies clearly showed that VAP related to MDR was associated with higher mortality rates, compared with VAP related to sensitive bacteria [30–32]. Several explanations

were suggested to explain the link between MDR and mortality, including higher rates of inappropriate antibiotic treatment, patient's underlying conditions, altered antimicrobial pharmacokinetic and high MICs, toxicity of last-resort antibiotics, and emergence of subsequent resistance [33].

Even though the incidence of VAT was lower in immunocompromised patients, the rate of progression from VAT to VAP was similar in immunocompromised and non-immunocompromised patients, suggesting that immunosuppression is not a risk factor for progression from VAT to VAP. The rate of progression from VAT to VAP was low in this study, probably because most of the patients with VAT received antibiotic treatment (92%). Interestingly, as in non-immunocompromised patients, the use of appropriate antibiotic treatment for VAT reduced the risk of progression towards VAP in immunocompromised patients. Appropriate antibiotic treatment was shown to be a protective factor in multivariate analysis for mortality risk in the TAVeM study [2]. Therefore, the early use of appropriate antibiotic treatment for tracheobronchitis in immunocompromised patients could be beneficial to reduce the transition from VAT to VAP and improve outcome [34]. However, only few studies focused on the antibiotic treatment for VAT [35, 36], and further large multicenter randomized controlled studies are required to clarify this issue [4].

In spite of similar rates of appropriate initial antibiotic treatment, immunocompromised patients with VA-LRTI had higher mortality rates than non-immunocompromised patients, mainly due to a higher mortality of immunocompromised patients with VAP. Further, immunosuppression was independently associated with ICU-mortality in patients with VA-LRTI. Previous studies reported higher associated-mortality rates in VAP patients [8, 37–39]. However, the mortality attributable to VAP is still a matter for debate, and is probably low [10]. In addition, the higher mortality of immunocompromised patients admitted to the ICU is already well described and is not surprising [17]. However, to our knowledge, no study has evaluated the relationship between mortality and immunosuppression in VAP patients.

Taken together, our results suggest that antibiotic treatment should be reduced and better tailored in immunocompromised patients, in order to prevent VAP related to MDR in this population. Further, preventive measures should probably be enhanced in immunocompromised patients, and appropriate initial antibiotic treatment should be the gold standard in these patients. Our data also suggest that large-spectrum antibiotic treatment should be given in immunocompromised patients with VA-LRTI, and that de-escalation should be performed as soon as possible, after receipt of microbiological results to break the vicious circle of overuse of antimicrobials and MDR emergence [40, 41]. However, further data are required on the relationship between de-escalation and outcome in immunocompromised patients [42]. The use of procalcitonin could be helpful to encourage physicians to perform de-escalation. Given the lower severity of VAT and the absence of impact on mortality, as compared with VAP, one could argue that VAT could be treated by shorter duration of antimicrobial treatment even in immunocompromised patients (Figure 2).

Our study has some limitations. Immunocompromised patients included many types of immunosuppression, and the number of patients with neutropenia was small. However, this is the first study on this particular population and we believe that our results are robust, and might be helpful for future research.

CONCLUSIONS

The incidence of VA-LRTI is significantly lower in immunocompromised patients, as compared with non-immunocompromised patients. These infections are more frequently caused by MDR in this population, and are associated with substantially higher mortality. These results suggest that prior antibiotic treatment should be better tailored in immunocompromised patients to reduce the incidence of MDR related infections. Further studies are required to better determine the relationship of type of immunosuppression and the risk for VA-LRTI.

REFERENCES

1. Craven DE, Hudcova J, Rashid J. Antibiotic therapy for ventilator-associated tracheobronchitis : a standard of care to reduce pneumonia , morbidity and costs ? *Curr. Opin. Pulm. Med.* 2015; 21: 250–259 Available from: http://www.ncbi.nlm.nih.gov/pubmed/25784245.

2. Martin-Loeches I, Povoa P, Rodríguez A, Curcio D, Suarez D, Mira J-PJ-PJ-P, Cordero MLML, Lepecq R, Girault C, Candeias C, Seguin P, Paulino C, Messika J, Castro AGAGAG, Valles J, Coelho L, Rabello L, Lisboa T, Collins D, Torres A, Salluh J, Nseir S, Fernández RO, Arroyo J, Gabriela M, Alvarez R, Reyes AT, Dellera C, Molina F, Franco DM, et al. Incidence and prognosis of ventilator-associated tracheobronchitis (TAVeM): a multicentre, prospective, observational study. *Lancet. Respir. Med.* 2015; 3: 859–868Available from: http://www.ncbi.nlm.nih.gov/pubmed/26472037.

3. Rodriguez A, Povoa P, Nseir S, Salluh J, Curcio D, Martin-Loeches I. Incidence and diagnosis of ventilator-associated tracheobronchitis (VAT) in the intensive care unit: an international online survey. *Crit Care* 2014; 18: R32Available from: http://www.ncbi.nlm.nih.gov/pubmed/24521533.

4. Nseir S, Povoa P, Salluh J, Rodriguez A, Martin-Loeches I. Is there a continuum between ventilator-associated tracheobronchitis and ventilator-associated pneumonia? *Intensive Care Med.* 2016; 42: 1190–1192Available from: http://www.ncbi.nlm.nih.gov/pubmed/27080532.

5. Nseir S, Di Pompeo C, Pronnier P, Beague S, Onimus T, Saulnier F, Grandbastien B, Mathieu D, Delvallez-Roussel M, Durocher a. Nosocomial tracheobronchitis in mechanically ventilated patients: Incidence, aetiology and outcome. *Eur. Respir. J.* 2002; 20: 1483–1489Available from: http://www.ncbi.nlm.nih.gov/pubmed/12503708.

6. Karvouniaris M, Makris D, Manoulakas E, Zygoulis P, Mantzarlis K, Triantaris A, Chatzi M, Zakynthinos E. Ventilator-associated tracheobronchitis increases the length of intensive care unit stay. *Infect. Control Hosp. Epidemiol.* 2013; 34: 800–808Available from: http://www.ncbi.nlm.nih.gov/pubmed/23838220.

7. Craven DE, Lei Y, Ruthazer R, Sarwar A, Hudcova J. Incidence and outcomes of ventilator-associated tracheobronchitis and pneumonia. *Am. J. Med.* 2013; 126: 542–549Available from: http://www.ncbi.nlm.nih.gov/pubmed/23561632.

8. Melsen WG, Rovers MM, Groenwold RHH, Bergmans DCJJ, Camus C, Bauer TT, Hanisch EW, Klarin

B, Koeman M, Krueger W a., Lacherade JC, Lorente L, Memish Z a., Morrow LE, Nardi G, van Nieuwenhoven C a., O'Keefe GE, Nakos G, Scannapieco F a., Seguin P, Staudinger T, Topeli A, Ferrer M, Bonten MJM. Attributable mortality of ventilator-associated pneumonia: A meta-analysis of individual patient data from randomised prevention studies. *Lancet Infect. Dis.* 2013; 13: 665–671Available from: http://www.ncbi.nlm.nih.gov/pubmed/23622939.

9. Parmentier-Decrucq E, Nseir S, Makris D, Desrousseaux B, Soudan B, Favory R, Mathieu D. Accuracy of leptin serum level in diagnosing ventilator-associated pneumonia: A case-control study. *Minerva Anestesiol.* 2014; 80.

10. Bekaert M, Timsit JF, Vansteelandt S, Depuydt P, Vésin A, Garrouste-Orgeas M, Decruyenaere J, Clec'h C, Azoulay E, Benoit D. Attributable mortality of ventilator-associated pneumonia: A reappraisal using causal analysis. *Am. J. Respir. Crit. Care Med.* 2011; 184: 1133–1139Available from: http://www.ncbi.nlm.nih.gov/pubmed/21852541.

11. Branch-Elliman W, Wright SB, Howell MD. Determining the Ideal Strategy for Ventilator-associated Pneumonia Prevention. Cost–Benefit Analysis. *Am. J. Respir. Crit. Care Med.* 2015; 192: 57–63Available from: http://www.ncbi.nlm.nih.gov/pubmed/25871807.

12. Melsen WG, Rovers MM, Bonten MJM. Ventilator-associated pneumonia and mortality: a systematic review of observational studies. *Crit. Care Med.* 2009; 37: 2709–2718Available from: http://www.ncbi.nlm.nih.gov/pubmed/19885994.

13. Darmon M, Ranzani OT, Azoulay E. Focus on immunocompromised patients. *Intensive Care Med.* 2018; in press Available from: http://link.springer.com/10.1007/s00134-017-4857-2.

14. Soares M, Bozza FA, Azevedo LCP, Silva UVA, Corrêa TD, Colombari F, Torelly AP, Varaschin P, Viana WN, Knibel MF, Damasceno M, Espinoza R, Ferez M, Silveira JG, Lobo SA, Moraes APP, Lima RA, de Carvalho AGR, do Brasil PEAA, Kahn JM, Angus DC, Salluh JIF. Effects of Organizational Characteristics on Outcomes and Resource Use in Patients With Cancer Admitted to Intensive Care Units. *J. Clin. Oncol.* 2016; 34: 3315–3324Available from: http://www.ncbi.nlm.nih.gov/pubmed/27432921.

15. Nseir S, Di Pompeo C, Diarra M, Brisson H, Tissier S, Boulo M, Durocher A. Relationship between immunosuppression and intensive care unit-acquired multidrug-resistant bacteria: a case-control study. *Crit. Care Med.* 2007; 35: 1318–1323Available from:

http://www.ncbi.nlm.nih.gov/pubmed/17414081.

16. Azoulay E, Lemiale V, Mokart D, Pène F, Kouatchet A, Perez P, Vincent F, Mayaux J, Benoit D, Bruneel F, Meert A-P, Nyunga M, Rabbat A, Darmon M. Acute respiratory distress syndrome in patients with malignancies. *Intensive Care Med.* 2014; 40: 1106–1114Available from: http://www.ncbi.nlm.nih.gov/pubmed/24898895.

17. Azoulay E, Mokart D, Pène F, Lambert J, Kouatchet A, Mayaux J, Vincent F, Nyunga M, Bruneel F, Laisne L-M, Rabbat A, Lebert C, Perez P, Chaize M, Renault A, Meert A-P, Benoit D, Hamidfar R, Jourdain M, Darmon M, Schlemmer B, Chevret S, Lemiale V. Outcomes of critically ill patients with hematologic malignancies: prospective multicenter data from France and Belgium--a groupe de recherche respiratoire en réanimation onco-hématologique study. *J. Clin. Oncol.* 2013; 31: 2810–2818Available from: http://ascopubs.org/doi/10.1200/JCO.2012.47.2365.

18. Lemiale V, Resche-Rigon M, Azoulay E, Study Group for Respiratory Intensive Care in Malignancies Groupe de Recherche en Réanimation Respiratoire du patient d'Onco-Hématologie. Early non-invasive ventilation for acute respiratory failure in immunocompromised patients (IVNIctus): study protocol for a multicenter randomized controlled trial. *Trials* 2014; 15: 372Available from: http://www.ncbi.nlm.nih.gov/pubmed/25257210.

19. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am. J. Respir. Crit. Care Med.* 2005; 171: 388–416Available from: http://www.ncbi.nlm.nih.gov/pubmed/15699079.

20. Paul M, Shani V, Muchtar E, Kariv G, Robenshtok E, Leibovici L. Systematic Review and Meta-Analysis of the Efficacy of Appropriate Empiric Antibiotic Therapy for Sepsis. *Antimicrob. Agents Chemother.* 2010; 54: 4851–4863Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2976147&tool=pmcentrez&rendertype=abstract.

21. Magiorakos A-P, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, Harbarth S, Hindler JF, Kahlmeter G, Olsson-Liljequist B, Paterson DL, Rice LB, Stelling J, Struelens MJ, Vatopoulos A, Weber JT, Monnet DL. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. *Clin. Microbiol. Infect.* 2012; 18: 268–281Available from: http://linkinghub.elsevier.com/retrieve/pii/S1198743X14616323.

22. Prentice RL, Kalbfleisch JD, Peterson A V, Flournoy N, Farewell VT, Breslow NE. The analysis of failure times in the presence of competing risks. *Biometrics* 1978; 34: 541–554Available from: http://www.ncbi.nlm.nih.gov/pubmed/373811.

23. Fine JP, Gray GR. A proportional hazards model for the subdistribution of a competing risk. 1999; 94: 496–509. *J Am Stat Assoc* 1999; 94: 496–509.

24. Acquarolo a., Urli T, Perone G, Giannotti C, Candiani a., Latronico N. Antibiotic prophylaxis of early onset pneumonia in critically ill comatose patients. A randomized study. *Intensive Care Med.* 2005; 31: 510–516Available from: http://www.ncbi.nlm.nih.gov/pubmed/15754197.

25. Sirvent JM, Torres A, El-Ebiary M, Castro P, De Batlle J, Bonet A. Protective effect of intravenously administered cefuroxime against nosocomial pneumonia in patients with structural coma. *Am. J. Respir. Crit. Care Med.* 1997; 155: 1729–1734Available from: http://www.ncbi.nlm.nih.gov/pubmed/9154884.

26. Vallés J, Peredo R, Burguenõ MJ, Rodrigues De Freitas a. P, Millań S, Espasa M, Martiń-Loeches I, Ferrer R, Suarez D, Artigas A. Efficacy of single-dose antibiotic against early-onset pneumonia in comatose patients who are ventilated. *Chest* 2013; 143: 1219–1225Available from: http://www.ncbi.nlm.nih.gov/pubmed/23715136.

27. Bassetti M, De Waele JJ, Eggimann P, Garnacho-Montero J, Kahlmeter G, Menichetti F, Nicolau DP, Paiva JA, Tumbarello M, Welte T, Wilcox M, Zahar JR, Poulakou G. Preventive and therapeutic strategies in critically ill patients with highly resistant bacteria. *Intensive Care Med.* 2015; 41: 776–795Available from: http://link.springer.com/10.1007/s00134-015-3719-z.

28. Martín-Loeches I, Diaz E, Vallés J. Risks for multidrug-resistant pathogens in the ICU. *Curr. Opin. Crit. Care* 2014; 20: 516–524Available from: http://www.ncbi.nlm.nih.gov/pubmed/25188366.

29. Garnacho-Montero J, Dimopoulos G, Poulakou G, Akova M, Cisneros JM, De Waele J, Petrosillo N, Seifert H, Timsit JF, Vila J, Zahar J-R, Bassetti M. Task force on management and prevention of Acinetobacter baumannii infections in the ICU. *Intensive Care Med.* 2015; Available from: http://www.ncbi.nlm.nih.gov/pubmed/26438224.

30. Depuydt PO, Vandijck DM, Bekaert M a, Decruyenaere JM, Blot SI, Vogelaers DP, Benoit DD. Determinants and impact of multidrug antibiotic resistance in pathogens causing ventilator-associated-pneumonia. *Crit. Care* 2008; 12: R142.

31. Martin-Loeches I, Torres A, Rinaudo M, Terraneo S, de Rosa F, Ramirez P, Diaz E, Fernández-Barat L, Li Bassi GL, Ferrer M. Resistance patterns and outcomes in intensive care unit (ICU)-acquired pneumonia. Validation of European Centre for Disease Prevention and Control (ECDC) and the Centers for Disease Control and Prevention (CDC) classification of multidrug resistant organi. *J. Infect.* 2015; 70: 213–222Available from: http://www.ncbi.nlm.nih.gov/pubmed/25445887.

32. Guillamet CV, Kollef MH. Update on ventilator-associated pneumonia. *Curr. Opin. Crit. Care* 2015; 21: 430–438Available from: http://www.ncbi.nlm.nih.gov/pubmed/26348421.

33. Barbier F, Lisboa T, Nseir S. Understanding why resistant bacteria are associated with higher mortality in ICU patients. *Intensive Care Med.* 2015; Available from: http://www.ncbi.nlm.nih.gov/pubmed/26564210.

34. Nseir S, Martin-Loeches I, Makris D, Jaillette E, Karvouniaris M, Valles J, Zakynthinos E, Artigas A. Impact of appropriate antimicrobial treatment on transition from ventilator-associated tracheobronchitis to ventilator-associated pneumonia. *Crit. Care* 2014; 18: R129Available from: http://www.ncbi.nlm.nih.gov/pubmed/24958136.

35. Palmer LB, Smaldone GC, Chen JJ, Baram D, Duan T, Monteforte M, Varela M, Tempone AK, O'Riordan T, Daroowalla F, Richman P. Aerosolized antibiotics and ventilator-associated tracheobronchitis in the intensive care unit. *Crit. Care Med.* 2008; 36: 2008–2013Available from: http://www.ncbi.nlm.nih.gov/pubmed/18552684.

36. Nseir S, Favory R, Jozefowicz E, Decamps F, Dewavrin F, Brunin G, Di Pompeo C, Mathieu D, Durocher A. Antimicrobial treatment for ventilator-associated tracheobronchitis: a randomized, controlled, multicenter study. *Crit. Care* 2008; 12: R62Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2481443&tool=pmcentrez&rendertype=abstract.

37. Kollef MH. Ventilator-associated pneumonia. A multivariate analysis. *JAMA* 1993; 270: 1965–1970Available from: http://www.ncbi.nlm.nih.gov/pubmed/8411554.

38. Messika J, Magdoud F, Clermont O, Margetis D, Gaudry S, Roux D, Branger C, Dreyfuss D, Denamur E, Ricard JD. Pathophysiology of Escherichia coli ventilator-associated pneumonia: Implication of highly virulent extraintestinal pathogenic strains. *Intensive Care Med.* 2012; 38: 2007–2016Available from: http://www.ncbi.nlm.nih.gov/pubmed/23052953.

39. Nair GB, Niederman MS. Ventilator-associated pneumonia: present understanding and ongoing debates. *Intensive Care Med.* 2014; 41: 34–48Available from: http://link.springer.com/10.1007/s00134-014-3564-5.

40. Garnacho-Montero J, Gutiérrez-Pizarraya A, Escoresca-Ortega A, Corcia-Palomo Y, Fernández-Delgado E, Herrera-Melero I, Ortiz-Leyba C, Márquez-Vácaro JA. De-escalation of empirical therapy is associated with lower mortality in patients with severe sepsis and septic shock. *Intensive Care Med.* 2014; 40: 32–40Available from: http://www.ncbi.nlm.nih.gov/pubmed/24026297.

41. Leone M, Bechis C, Baumstarck K, Lefrant J-Y, Albanèse J, Jaber S, Lepape A, Constantin J-M, Papazian L, Bruder N, Allaouchiche B, Bézulier K, Antonini F, Textoris J, Martin C, AZUREA Network Investigators. De-escalation versus continuation of empirical antimicrobial treatment in severe sepsis: a multicenter non-blinded randomized noninferiority trial. *Intensive Care Med.* 2014; 40: 1399–1408Available from: http://www.ncbi.nlm.nih.gov/pubmed/25091790.

42. Mokart D, Slehofer G, Lambert J, Sannini A, Chow-Chine L, Brun J-P, Berger P, Duran S, Faucher M, Blache J-L, Saillard C, Vey N, Leone M. De-escalation of antimicrobial treatment in neutropenic patients with severe sepsis: results from an observational study. *Intensive Care Med.* 2014; 40: 41–49Available from: http://www.ncbi.nlm.nih.gov/pubmed/24231857.

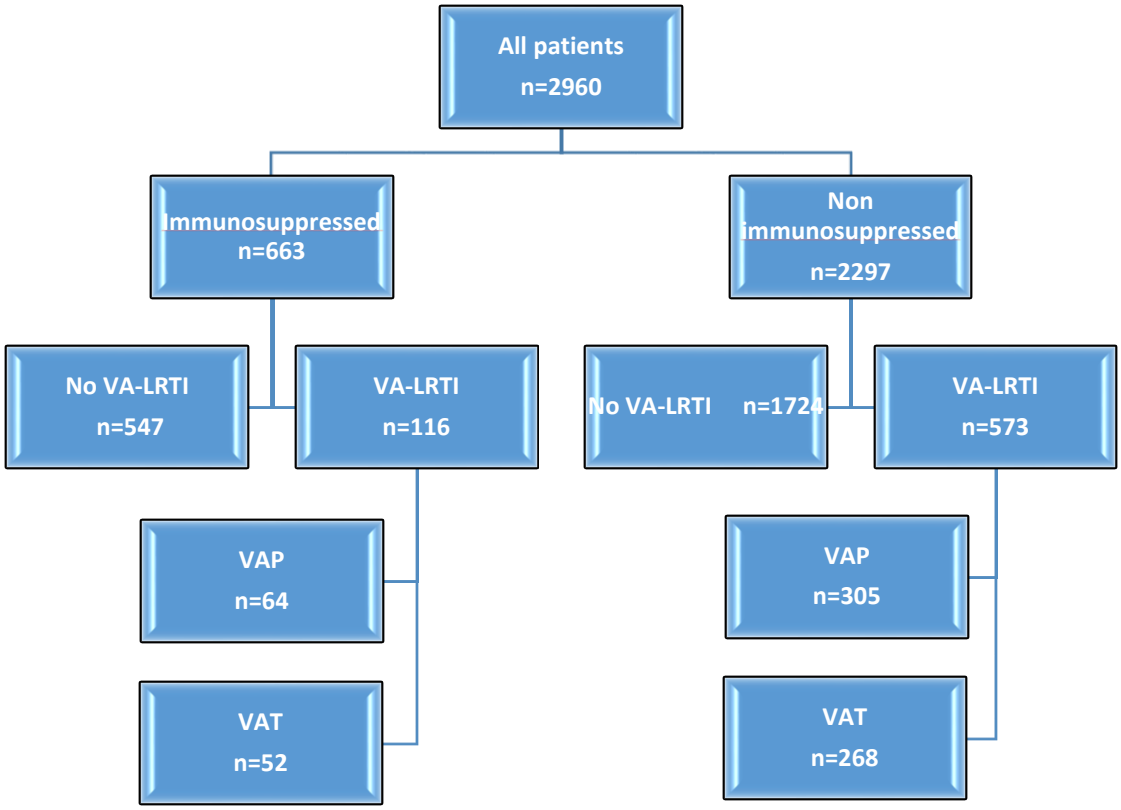

Figure 1

Study flowchart

VA-LRTI: ventilator-associated lower respiratory tract infections; VAT: ventilator-associated tracheobronchitis; VAP: ventilator-associated Pneumonia

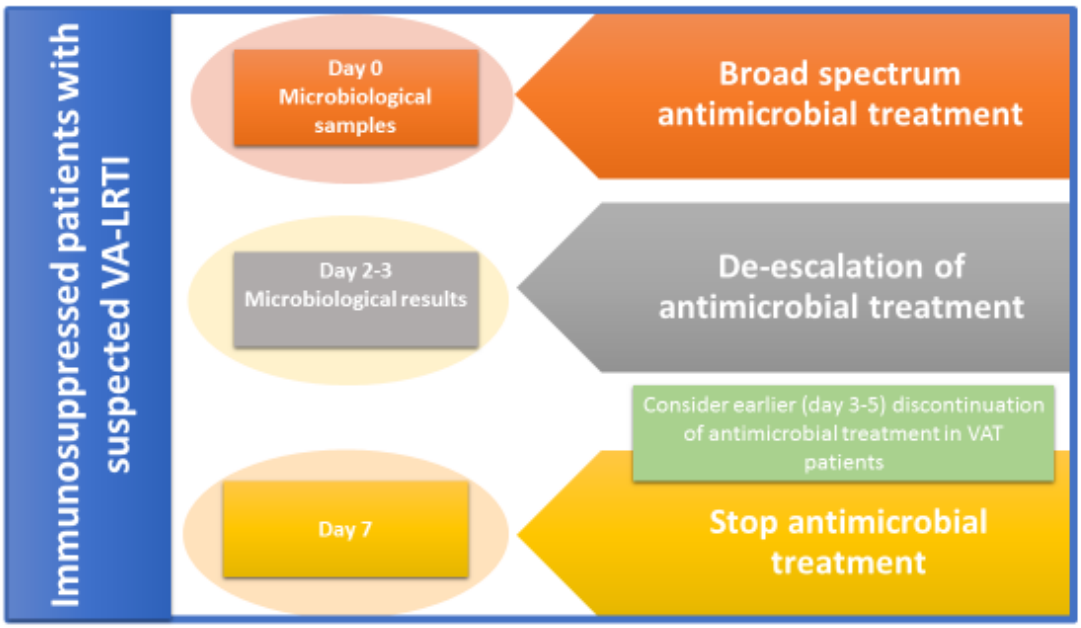

Figure 2

Suggested algorithm for antibiotic treatment in immunosuppressed patients with ventilator-associated lower respiratory tract infections.

VA-LRTI, ventilator-associated lower respiratory tract infections; VAT, ventilator-associated tracheobronchitis

Table 1. Types of immunosuppression (n=663).

	n	%*
Nonmetastatic solid cancer	296	45
Immunosuppressive drug	296	45
Hematological malignancy	123	19
Metastatic solid cancer	112	17
HIV	49	7
Organ transplant	28	4
Allogeneic HSCT	25	4

HIV, human immunodeficiency virus; HSCT: hematopoietic stem cell transplant

*Total percentage is higher than 100% because several patients had more than one type of immunosuppression

Table 2. Patient characteristics

	Immunosuppression		
	Yes n = 663	**No n = 2297**	***p***
Age	63±15	61±17	0.020
Male gender	407 (61)	1442 (63)	0.51
SAPS2	53±19	50±19	0.001
SOFA	8±4	8±4	0.031
Chronic disease			
Diabetes mellitus	125 (22)	443 (19)	0.80
Alcohol abuse	64 (10)	294 (13)	0.028*
Chronic respiratory failure	62 (9)	224 (10)	0.76
COPD	113 (17)	381 (17)	0.78
Chronic kidney disease	88 (13)	205 (9)	0.001*
Cirrhosis	40 (6)	137 (6)	0.95
Category of admission			<0.001
Medical	453 (68)	1435 (63)	
Surgical	165 (25)	379 (17)	
Trauma	45 (7)	483 (21)	

Results are n (%), or mean±SD

VA-LRTI, ventilator-associated lower respiratory tract infection; VAT: ventilator-associated tracheobronchitis; VAP: ventilator-associated pneumonia

*OR (95% CI) 0.72 (0.55-0.97), 1.56 (1.20-2.04); respectively

Table 3. Incidence of ventilator-associated lower respiratory tract infections.

	Immunosuppression			
	Yes n = 663	**No n = 2297**		
			p	**SHR (95% CI)**
VA-LRTI	116 (16.6)	573 (24.2)	<0.0001	0.65 (0.53-0.80)
VAT	52 (7.3)	268 (11.6)	0.002	0.61 (0.45-0.84)
VAP	64 (9.3)	305 (12.7)	0.019	0.72 (0.54-0.95)

Results are number of events (cumulative incidence rate in %, calculated using competing approach). SHRs were calculated based on Fine-Gray model, using extubation and death as competing events.

SHR, sub-hazard ratio; VA-LRTI: ventilator-associated lower respiratory tract infection; VAT: ventilator associated tracheobronchitis; VAP: ventilator-associated pneumonia

Table 4. Outcomes of study patients.

	Immunosuppression Yes n= 663				No n= 2297			
	VAT **n = 52**	**VAP** **n = 64**	**No VA-LRTI** **n = 547**	**p**	**VAT** **n =268**	**VAP** **n = 305**	**No VA-LRTI** **n = 1724**	**p**
MV duration, days (median, IQR)	16 (10-25.5)	15 (8-27)	7 (4-14)	<0.0001	13 (8-22)	14 (8-26)	7 (4-12)	<0.0001
ICU length of stay, days (median, IQR)	23 (16-38)	20 (13-30)	12 (7-20)	<0.0001	21 (14-33)	21 (13-34)	12 (8-19)	<0.0001
ICU mortality, n (%)	22 (42)	41 (64)*	216 (39)	0.001	71 (27)	105 (34)	487 (28)	0.016

Results are n (%), or median (interquartile range)

MV, Mechanical Ventilation; VA-LRTI, ventilator-associated lower respiratory tract infection; VAT, ventilator-associated tracheobronchitis; VAP, ventilator-associated pneumonia

p-value are for comparisons between the three groups

*p <0.001, OR (95% CI) 3.4 (1.93-5.96) vs VAP in patients with no immunosuppression

Table 5. Risk factors for ICU-mortality in patients with ventilator-associated lower respiratory tract infection using Cox proportional hazards regression analysis.

Multivariate analysis	P	Hazard ratio (95% CI)
Age	0.005	1.01 (1.003-1.01)*
Immunosuppression	0.002	1.6 (1.19-2.16)
SOFA score at VA-LRTI diagnosis	<0.001	1.04 (1.03-1.06)*
Appropriate antibiotic treatment	0.005	0.61 (0.44-0.86)

SOFA, sequential organ failure assessment, VA-LRTI, ventilator-associated lower respiratory tract infection.

*Per year and per point, respectively.

The TAVeM study group included the following contributors:

Ignacio Martín-Loeches, Alejandro Rodriguez, Daniel Curcio, Rubén Oscar Fernández, Jorge Arroyo, Maria Gabriela, Rodriguez Alvarez, Alex Tamayo Reyes, Christian Dellera, Francisco Molina, Daniel Molano Franco, Edwin Giovanny Chapeta Parada, Estuardo Salgado Yepez, Fernando Paredes Oña, Diego Morocho Tutillo , Diego Barahona , Francisco Alvarez Lerma, Ana Abella Álvarez, Jose Manuel Allegue Gallego, Francisco José Fuentes Morillas, Antonio Luis Ruiz Aguilar, María Lourdes Cordero Lorenzana, Rafael Sanchez Iniesta, Jordi Almirall , Antonio Albaya , Sergio Ruiz Santana, Carmen Fernandez , Miguel Angel Blasco Naval Potro, Pablo Vidal Cortes, Belen Jimenez , Rafael Sierra , Maria Del Valle Ortiz, Nieves Cruza , Pedro Maria Olaechea , Ana Carolina Caballero Zirena, Pilar Posada Gonzalez, Teresa Recio Gomez, Lorenzo Socias Crespi, Paula Ramírez Galleymore, Ricard Jordà Marcos, César Palazón, Bernardo Gil Rueda, Juan Carlos Ballesteros, Maria Pilar Gracia Arnilla, Antonia Socias , Joaquin Amador , Esperanza Molero Silvero, Laura Macaya Redín, Mónica Zamora Elson, Luis Cabré Pericas, Joaquín Álvarez Rodríguez, Mercedes Nieto , Antoni Torres, Elena Molinos, Ana Josefina, Nuno Catorze, Pedro Póvoa , Carlos Candeias , Luis Coelho , Paulo André , José Andrade Gomes, Elisa Vedes, Antero Fernandes, Miguel Ángel García, Catalina Sanchez Ramirez, Milagros Calizaya, Angel Estella, Adrià Albis, Gerardo Aguilar, Eva Torrents, Marta Gurpegui Puente, Angel Gabriel Sanchez, Thiago Lisboa, Pedro Azambuja , Marcos Freitas Knibel, Otavio Ranzani , Laura Darriba W. Camargo, Antonio Paulo Nassar Junior, Cesar Biselli Ferreira, Suzana Lobo , Ligia Rabello, Marcelo Park , Alexandre Guilherme Ribeiro de Carvalho, Mauricio Valencia, Alejandro Gonzalez Castro, Adoración Alcalá López, José María Castillo Caballero, Saad Nseir, Karim Jaffal, Erika Parmentier-Decrucq, Sébastien Préau, Chloé Rousselin, Caroline Blazejewski, Juliette Masse, Laurent Robriquet, Léa Satre-Buisson, Jean-Paul Mira, Nathalie Martin, Raphael Lepecq, Hervé Mentec, Christophe Girault, Antoine Marchalot, Jonathan Messika, Jean-Damien Ricard, Philppe Seguin, Bruno Mégarbane, Sandrine Valade, Elie Azoulay, Nicolas Boussekey, Olivier Leroy, Jean Reignier, Marc Clavel, Nicolas Pichon, Thomas Baudry, Laurent Argaud, Pascal Beuret,

Ali Ait-Hssain, Martine Nyunga, Isabelle Alves, Florent Dewavrin, Guillaume Brunin, Stéphane Mérat, Pierre Pasquier, Frédéric Brun, Aurore Palud, Benoit Voisin, Romaric Grenot, Nicolas Van Grunderbeeck, Didier Thévenin, Benoit Misset, François Philippart, Jean-Pierre Frat, Rémi Coudroy, Philippe Cabaret, Marie Ledein, Fethi Zoheir Hadj Slimane, Romain Miguel-Montanes, Nicolas Weiss, Francis Bolgert, Bernard Just.

Online supplementary material

RESULTS

Main reasons for ICU admission are presented in Table 1.

Diagnostic procedure

In IC patients, the percentage of endotracheal aspirate and bronchoalveolar lavage was significantly higher in VAP than in VAT patients. In non-IC patients, although the percentage of endotracheal aspirate was significantly lower in VAP than in VAT patients; the percentage of bronchoscopy, bronchoalveolar lavage, mini bronchoalveolar lavage, and blood cultures were significantly higher in VAP than in VAT patients (Table 2).

Microorganisms

Although the percentage of patients with VA-LRTI related to MDR, Enterobacter spp., and MRSA was significantly higher in IC patients than in non-IC patients; the percentage of patients with VA-LRTI related to MSSA was significantly lower in IC patients than in non-IC patients (Table 3).

In the VAT subgroup, the only difference between IC patients and non-IC patients was a higher incidence of *Enterobacter* spp. in IC patients than in non-IC patients (19.2 versus 9.3%, p=0.05). However, in the VAP subgroup, the incidence of MRSA and *Enterobacter* spp. was significantly higher in IC patients than in non-IC patients (6.3% versus 1.3 %, p=0.033; 21.9% versus 10.5%, p=0.02; respectively); whereas MSSA incidence was significantly lower in IC patients than in non-IC patients (3.1% versus 25.6%, p<0.001).

Risk factors for ICU-mortality in patients with VA-LRTI by univariate analysis

At ICU admission, age, SAPS II, SOFA, immunosuppression, and admission category were significantly associated with higher ICU-mortality rate in these patients. At VA-LRTI diagnosis, SOFA score, MDR, were associated with increased ICU-mortality. Appropriate antibiotic treatment was associated with significantly lower ICU-mortality rate (Table 4).

Table 1. Main reasons for ICU admission

	Immunosuppression Yes	No	p
	n = 663	n = 2297	
Acute respiratory distress syndrome	99 (4.3)	48 (7.2)	0.01
Acute exacerbation of COPD	110 (4.8)	13 (2)	<0.001
Pneumonia	282 (12.3)	136 (20.5)	<0.001
Aspiration	40 (1.7)	9 (1.4)	0.60
Pulmonary embolism	14 (0.6)	7 (0.1)	0.29
Pleural effusion	4 (0.2)	5 (0.8)	0.03
Pneumothorax	8 (0.3)	3 (0.5)	0.72
Hemothorax	15 (0.7)	3 (0.5)	0.78
Sepsis	226 (9.8)	112 (17)	0.001
Shock	198 (8.6)	71 (11)	0.07
Agina pectoris	11 (0.5)	2 (0.3)	0.74
Abdominal aortic aneurysm	12 (0.5)	2 (0.3)	0.74
Cardiomyopathy	25 (1.1)	4 (0.6)	0.37
Congestive heart failure	84 (3.6)	12 (1.8)	0.02
Arrhythmia	30 (1.3)	4 (0,6)	0.15
Myocardial inafrction	63 (2.7)	6 (0.9)	0.01
Rupture of esophageal varices	9 (0.4)	0 (0)	0.22
Gastrointestinal bleeding	29 (1.3)	4 (0.6)	0.21
Liver failure	30 (1.3)	4 (0.6)	0.15
Pancreatitis	34 (1.5)	2 (0.3)	0.01
Acute renal failure	32 (1.4)	13 (2)	0.28

Overdose	29 (1.3)	1 (0.2)	0.01
Seizure	56 (2.4)	15 (2,3)	0.89
Coma	232 (10.1)	44 (6.6)	0.01
Empyema	2 (0.1)	0 (0)	1.00
Stroke	110 (4.8)	11 (1.6)	<0.001
Brain aneurysm	37 (1.6)	5 (0.8)	0.13
Brain death	5 (0.2)	2 (0.3)	0.66
Transient ischemic attack	2 (0.1)	0 (0)	1,00
Traumatic brain injury	155 (6.7)	4 (0.6)	<0.001
Other	262 (11.4)	101 (15.2)	0.01

COPD, chronic obstructive pulmonary disease

Table 2. Diagnostic procedures in patients with ventilator-associated lower respiratory tract infections.

	Immunosuppression					
	Yes n = 116			No n = 573		
	VAT n = 64	VAP n = 52	p	VAT n = 268	VAP n = 305	p
Endotracheal aspirate	43 (67)	42 (81)	0.039*	235 (88)	211 (69)	<0.001*
Blind protected specimen brush	5 (8)	11 (21)	0.29	27 (10)	40 (13)	0.3
Bronchoscopy	3 (5)	11 (21)	0.085	17 (6)	45 (15)	0.001*
Bronchoalveolar lavage	4 (6)	14 (27)	0.042*	11 (4)	45 (15)	<0.001*
Mini bronchoalveolar lavage	3 (5)	5 (10)	0.73	14 (5)	40 (13)	0.001*
Blood cultures	31 (48)	45 (87)	0.25	155 (58)	230 (75)	<0.001*
Tested for *Streptococcus pneumoniae* antigen	2 (3)	6 (12)	0.29	12 (4)	10 (3)	0.46
Tested for *Legionella pneumophila* antigen	3 (5)	7 (13)	0.51	11 (4)	14 (5)	0.78

Data are numbers (%)

IC, immunocompromised; VAT, ventilator-associated tracheobronchitis; VAP, ventilator-associated pneumonia

* OR (95% CI): 2.5 (1.03-6.1); 3.17 (2.04-4.91); 0.39 (0.22-0.70); 0.3 (0.0.09-0.97); 0.28 (0.13-0.49); 0.37 (0.19-0.69); 0.45 (0.31-0.64); respectively

Table 3. Microorganisms in patients with ventilator-associated lower respiratory tract infections

	Immunosuppression		P
	Yes n = 116	No n = 573	
Polymicrobial	25 (22)	114 (20)	0.7
MDR	83 (72)	338 (59)	0.011*
Gram-negative bacilli	117	509	
Pseudomonas aeruginosa	33 (28)	135 (24)	0.26
Enterobacter sp.	24 (21)	57 (10)	0.001*
Klebsiella sp.	16 (14)	85 (15)	0.77
Escherishia coli	16 (14)	61 (11)	0.33
Stenotrophomonas maltophilia	7 (6)	24 (4)	0.38
Acinetobacter baumannii	7 (6)	34 (6)	0.97
Serratia marcescens	3 (3)	25 (4)	0.37
Proteus mirabilis	4 (3)	25 (4)	0.66
Hemophilus influenzae	5 (4)	52 (9)	0.089
Citrobacter freundii	2 (2)	11 (2)	0.89
Gram-positive Cocci	24	178 (31)	
Streptococcus pneumoniae	8 (7)	32 (6)	0.58
MSSA	10 (9)	136 (24)	<0.001*
MRSA	6 (5)	10 (2)	0.025*

Data are numbers (%)

MDR, multidrug-resistant bacteria; MSSA, methicillin-sensitive *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*

*OR (95% CI): 1.75 (1.13-2.71); 2.36 (1.4-4); 0.3 (0.15-0.6); 3.1 (1.1-8.62)

Table 4. Risk factors for ICU mortality in patients with ventilator-associated lower respiratory tract infection by univariate analysis.

	Survivors n = 450	Nonsurvivors n = 239	P
At ICU admission			
Age	59 (44, 71)	66 (57, 77)	<0.001
Male gender	306	157	0.54
SAPS II	45 (34, 58)	54 (42, 65)	<0.001
SOFA	7 (5, 10)	8 (6, 11)	0.002
Immunosuppression	53	63	<0.001
ARDS	36	28	0.11
Category of admission			<0.001
Medical	233	160	
Surgical	66	35	
Trauma	151	44	
At VA-LRTI diagnosis			
SOFA	6 (4, 8)	9 (6, 11)	<0.001
Appropriate antibiotic treatment	400	194	0.005*
Multidrug resistant bacteria	256	165	0.001*

Data are numbers (%) or median (interquartile range)

ICU, intensive care medicine; SAPS, simplified acute physiology score; SOFA, sequential organ failure assessment; ARDS, acute respiratory distress syndrome; VA-LRTI, ventilator-associated lower respiratory tract infection

*OR (95% CI): 0.54 (0.39-0.86), 1.72 (1.23-2.4)