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

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

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

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

Incidence of VA-LRTI was significantly lower among immunocompromised patients, but it was associated with a significantly higher mortality rate. Multidrug-resistant pathogens were more frequently found in immunocompromised patients with VA-LRTI.

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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 colonisation of the lower respiratory tract and VAP [3, 4]. This infection is associated with higher rates of subsequent VAP, and prolonged duration of mechanical ventilation [5–7]. Recently, our group have shown that VAT is a separate entity, responsible for the increased duration of mechanical ventilation and increased 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 have demonstrated that VAP is 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 broad-spectrum antibiotic treatment, thus increasing the risk for developing multidrug-resistant bacteria (MDR) [15]. The main cause of admission to the ICU for these patients is acute respiratory failure [16]. Although their outcomes have substantially improved in recent years, the prognosis remains poor, with hospital mortality rates of 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 hypothesised that immunocompromised patients would develop more VA-LRTI than non-immunocompromised patients, given the context of altered host defences. Therefore, we conducted this study to determine the incidence, aetiology and outcome of these infections in immunocompromised patients, and to determine if these factors are different in 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 >18 years admitted to 114 ICUs in Europe and Latin America receiving mechanical ventilation for >48 h between September 1, 2013 and July 31, 2014 [2].

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

Patients considered to be immunocompromised were those with ongoing neoplasia, haematological malignancy, AIDS, an allogeneic stem cell transplant, an organ transplant or taking immunosuppressive drugs [18].

Procedures and definitions

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

The diagnosis of VA-LRTI was based on the presence of at least two of the following criteria: body temperature <36·5°C or >38·5°C, leukocyte count <4000 cells·μL^{-1} or >12 000 cells·μL^{-1}, and purulent endotracheal aspirate. To be included in the final analysis, all episodes of infection had to have a positive microbiological isolation in the endotracheal aspirate of at least 10^5 CFU·mL^{-1}, or in bronchoalveolar lavage fluid of at least 10^4 CFU·mL^{-1}.

VAT was defined with the aforementioned criteria with no radiographic signs of new infiltrate; VAP was defined by the presence of new or progressive infiltrate on chest radiography. VAP was deemed to occur subsequently to VAT if it was diagnosed in the 96 h period after diagnosis of tracheobronchitis and if the same microorganism caused both infections. VAP was considered to be early-onset when it was diagnosed <5 days, and late-onset when it was diagnosed ⩾5 days, 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 the aetiology 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 the progression from VAT to VAP in immunocompromised patients as compared to in non-immunocompromised patients.

Statistical analysis

We used SPSS software (version 22; SPSS Inc., IBM, New York, NY, USA) for data analysis. The incidence, aetiology 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 mean±SD and skewed continuous variables as medians (interquartile range (IQR)). We used Chi-squared tests or Fisher's exact test to compare qualitative variables, and 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 significant if $p<0.05$.

The cumulative incidence of VA-LRTI was estimated using extubation and death as competing risks, based on the approach of Prentice *et al.* [22]. The cumulative incidence of VA-LRTI was compared between immunocompromised and non-immunocompromised patients using the Fine–Gray model [23]. Sub-hazard ratios (SHRs) were derived from these models, because effect size and proportional sub-hazards assumptions 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 a p-value <0.1 by univariate analysis were included in a Cox proportional hazards regression model using a stepwise backwards 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 known immunosuppression, owing mainly to non-metastatic solid cancer or immunosuppressive drug use (table 1, figure 1). Age, Simplified Acute Physiology Score II, Sequential Organ Failure Assessment score, percentage of patients with chronic kidney disease and medical category of admission were significantly higher among immunocompromised patients than among non-immunocompromised patients. The percentage of patients with a history of alcohol abuse was significantly lower among immunocompromised patients than among non-immunocompromised patients. No significant difference was found between the two groups for other patient characteristics (table 2). Reasons for ICU admission are summarised in the supplementary material.

TABLE 1 Types of immunosuppression

	n (%)
Non-metastatic solid cancer	296 (45)
Immunosuppressive drug	296 (45)
Haematological malignancy	123 (19)
Metastatic solid cancer	112 (17)
HIV	49 (7)
Organ transplant	28 (4)
Allogeneic HSCT	25 (4)
Total n	663[#]

HSCT: haematopoietic stem cell transplant. [#]: total percentage is higher than 100% because several patients had more than one type of immunosuppression.

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

Incidence of VA-LRTI

The incidence of VA-LRTI was significantly lower among immunocompromised patients than among non-immunocompromised patients. Similarly, the incidence of VAT or VAP was significantly lower among immunocompromised patients than among 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%) *versus* 229 of 568 (40%); p=0.33). Similar results were found in the subgroups of patients with VAT (16 of 52 (31%) *versus* 101 of 267 (38%); p=0.32) and with VAP (20 of 64 (31%) *versus* 128 of 302 (42%); p=0.099).

Multidrug-resistant bacteria

In patients with VA-LRTI, the rate of MDR bacteria was significantly higher among immunocompromised patients than among non-immunocompromised patients (83 of 116 (72%) *versus* 338 of 573 (59%);

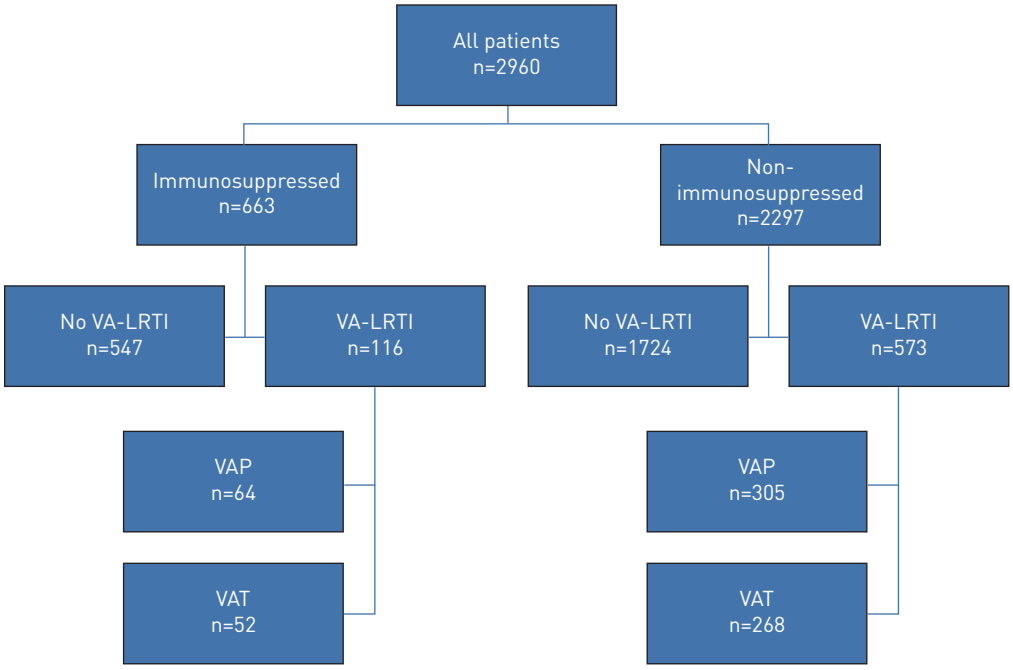

FIGURE 1 Study flowchart. VA-LRTI: ventilator-associated lower respiratory tract infections; VAP: ventilator-associated pneumonia; VAT: ventilator-associated tracheobronchitis.

TABLE 2 Patient characteristics

	Immunosuppression		p-value
	Yes	No	
Subjects n	663	2297	
Age years	63±15	61±17	0.020
Male sex	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)	

Data are presented as n (%) or mean±SD, unless otherwise stated. SAPS2: Simplified Acute Physiology Score II; SOFA: Sequential Organ Failure Assessment score; COPD: chronic obstructive pulmonary disease. #: OR 0.72, 95% CI 0.55–0.97; ¶: OR 1.56, 95% CI 1.20–2.04.

OR 1.75, 95% CI 1.13–2.71; p=0.011). Similar results were found in the subgroup of patients with VAP (49 of 64 (78%) *versus* 176 of 305 (58%); OR 2.39, 95% CI 1.29–4.48; p=0.005), but not in VAT patients (34 of 52 (65%) *versus* 162 of 268 (60%); p=0.52).

Among patients with VA-LRTI, methicillin-resistant *Staphylococcus aureus* and *Enterobacter* spp. were significantly more frequent in immunocompromised patients than in non-immunocompromised patients; however, methicillin-sensitive *Staphylococcus aureus* was significantly less frequent in immunocompromised patients than in 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 between immunocompromised and non-immunocompromised patients (7 of 52 (13%) *versus* 32 of 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 of 52 (75%) received appropriate antibiotics. The percentage of immunocompromised patients with progression from VAT to VAP was significantly lower in patients

TABLE 3 Incidence of ventilator-associated lower respiratory tract infections

	Immunosuppression			
	Yes	No	p-value	SHR (95% CI)
Subjects n	663	2297		
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)

Data are presented as number of events (cumulative incidence rate in %, calculated using competing approach), unless otherwise stated. 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[#]				No[¶]			
	VAT	VAP	No VA-LRTI	p-value	VAT	VAP	No VA-LRTI	p-value
Subjects n	52	64	547		268	305	1724	
MV duration days	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	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)	457 (27)	0.016

Data are presented as median (interquartile range), unless otherwise stated. p-values are for comparisons between the three groups. VAT: ventilator-associated tracheobronchitis; VAP: ventilator-associated pneumonia; VA-LRTI: ventilator-associated lower respiratory tract infection; MV: mechanical ventilation; ICU: intensive care unit. [#]: n=663; [¶]: n=547; [+]: OR 3.4, 95% CI 1.93–5.96 *versus* VAP in patients with no immunosuppression; p<0.001.

who received appropriate antibiotic treatment than in those who received inappropriate antibiotic treatment (3 of 39 (8%) *versus* 4 of 13 (31%); OR 0.19, 95% CI 0.035–0.992; p=0.035).

Impact of immunosuppression on VA-LRTI outcomes

Among patients with VA-LRTI, ICU mortality rate was higher among immunocompromised patients than among non-immunocompromised patients (54% *versus* 30%; OR 2.68, 95% CI 1.78–4.02; p<0.0001). 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 was 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 supplementary material.

Discussion

Our results show that the incidence of VA-LRTI was significantly lower among immunocompromised patients than among non-immunocompromised patients. Additionally, immunocompromised patients more frequently received previous antibiotic treatment and developed VAP related to MDR bacteria than did non-immunocompromised patients. The development of VAT or VAP in immunocompromised patients was associated with increased duration of mechanical ventilation, and VAP was associated with significantly increased ICU mortality, as 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 multicentre international 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 under-diagnosed these infections because of neutropenia, but only nine patients had neutropenia in our

TABLE 5 Risk factors for intensive care unit mortality in patients with ventilator-associated lower respiratory tract infection using Cox proportional hazards regression analysis

Multivariate analysis	p-value	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; [¶]: per point.

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 the 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 randomised controlled and observational studies suggested that antibiotic treatment in mechanically ventilated patients with coma was associated with a 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 show that VAP related to MDR is associated with higher mortality rates than VAP related to sensitive bacteria [30–32]. Several explanations have been 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 minimum inhibitory concentrations, toxicity of last-resort antibiotics and emergence of subsequent resistance [33].

Even though the incidence of VAT was lower among immunocompromised patients, the rate of progression from VAT to VAP was similar between 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 patient outcomes [34]. However, few studies have focused on antibiotic treatment for VAT [35, 36], and further large multicentre randomised 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 higher mortality among immunocompromised patients with VAP. Further, immunosuppression was independently associated with ICU mortality among patients with VA-LRTI. Previous studies reported higher associated-mortality rates among 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 among immunocompromised patients admitted to the ICU is already well described and is not surprising [17]. 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 to prevent VAP related to MDR in this population. Further, preventive

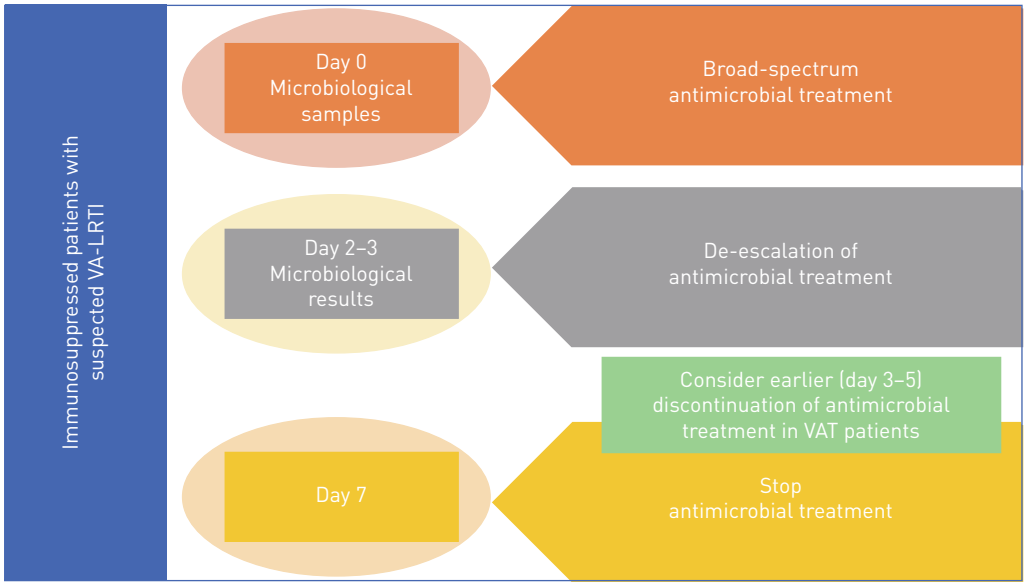

FIGURE 2 Suggested algorithm for antibiotic treatment in immunosuppressed patients with ventilator-associated lower respiratory tract infections (VA-LRTI). VAT: ventilator-associated tracheobronchitis.

measures should be enhanced in immunocompromised patients, and appropriate initial antibiotic treatment should be the gold standard in these patients. Our data also suggest that broad-spectrum antibiotic treatment should be given to 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, as compared with VAP, and the absence of impact on mortality, one could argue that VAT could be treated by a shorter duration of antimicrobial treatment even in immunocompromised patients (figure 2).

Our study has some limitations. Our immunocompromised group included patients with 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 among immunocompromised patients than among 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 between the type of immunosuppression and the risk for VA-LRTI.

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