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Running title

Predictive factors of MSSA-VAP relapse

Ethics approval

The data file was declared to the French Data Protection Agency (CNIL, N° 1925005) and the study was approved by the institutional review board (IRB 00006477) of Bichat hospital, Paris 7 University, AP-HP.

Invitation

This paper is not an invited paper.

Total word count

2818 words

Conflicts of interest/Competing interests disclosure

Maxens Decavèle, Nathalie Gault, Jean Denis Moyer, Maël Gennequin, Pierre-Antoine Allain and Arnaud Foucrier had no conflicts of interest to declare.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author's contributions to the manuscript

A : Conceptualization/Methodology

B : Analysis/Statistics-software

C : Data acquisition/curation

D : Data interpretation

E : Writing original draft

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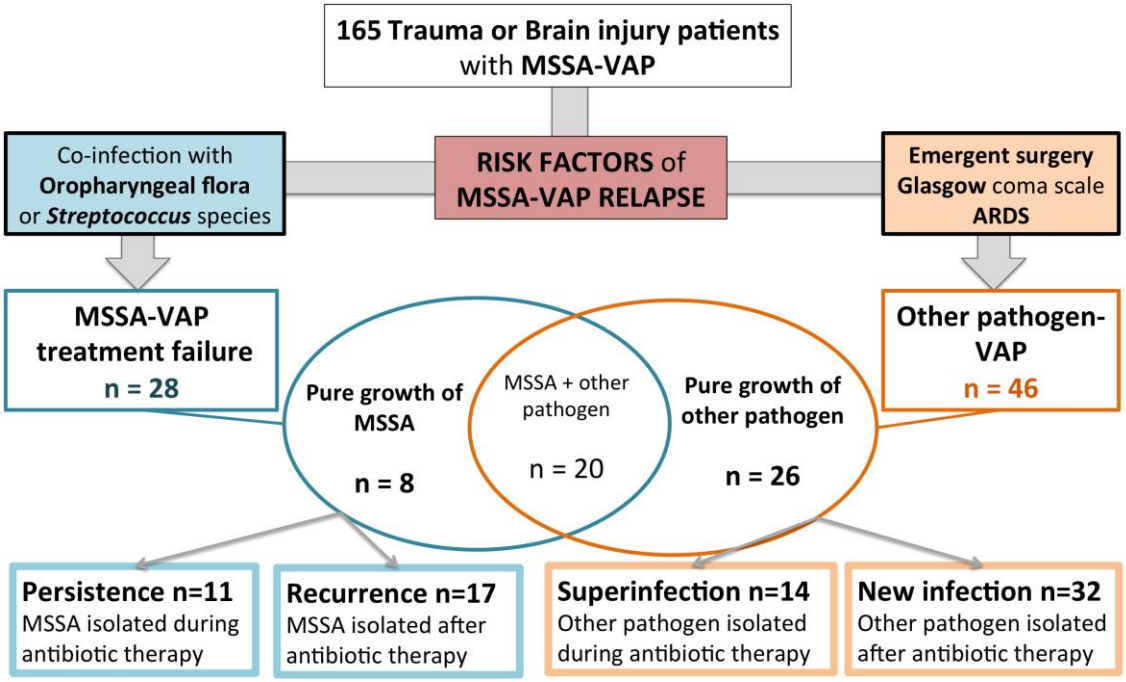
Abstract

Purpose: To describe the incidence and risk factors of methicillin sensitive staphylococcus aureus ventilator associated pneumonia (MSSA-VAP) relapse in trauma and non-traumatic brain injury patients.

Materials and Methods: Retrospective observational monocentric cohort study of consecutive ICU patients who developed a first episode of MSSA-VAP after trauma and non-traumatic brain injury. MSSA-VAP relapse encompass MSSA-VAP treatment failure (persistence or recurrence of MSSA) or other pathogen - VAP.

Results: A total of 165 patients (71% of trauma and 29% of non-traumatic brain injury) with MSSA-VAP were included. MSSA-VAP relapse occurred in 54 (33%) patients, including 28 (17%) MSSA-VAP treatment failure and 46 (28%) other pathogen-VAP. Empirical first-line antibiotic therapy was appropriate in 96% of cases. In multivariate analysis, the presence of Streptococcus species (Odds ratio [OR] 7.37) and oropharyngeal flora (OR 3.64) as initial MSSA co-pathogen, suggested aspiration at the time of admission and independently predicted MSSA-VAP treatment failure. Initial Glasgow coma scale (OR 0.89), need for emergent surgery (OR 5.71) and the presence of an acute respiratory distress syndrome at the time of the first MSSA-VAP (3.99), independently predicted the onset of other pathogen – VAP.

Conclusion: Early and simple factors may help to identify patients with high-risk of MSSA-VAP relapse.



Key words

Ventilator associated pneumonia

Methicillin Sensitive Staphylococcus Aureus (MSSA)

Ventilator associated pneumonia relapse

Trauma

Brain injury patient

Introduction

Ventilator associated pneumonia (VAP), defined by an intensive care unit (ICU) acquired pneumonia that develops in patients mechanically ventilated for at least 48 h [1], is the most common complication in patients receiving invasive mechanical ventilation. Although VAP incidence have significantly decreased in the general ICU population and currently concerns around 10% of intubated ICU patients [2], its incidence remains very high in trauma and non-traumatic brain injury (NTBI) patients (around 50%) [3-6]. Consciousness disorders and subsequent aspiration at the time of brain injury, inflammatory response [7] and prolonged mechanical ventilation, especially in case of severe brain injury, could explain this finding. Whereas gram-negative bacterial strains are prevalent in VAP of non-trauma patients [1, 2, 8], methicillin-sensible *Staphylococcus aureus* (MSSA) is the pathogen the most frequently encountered in VAP of trauma and NTBI patients, accounting for up to 40-50% of VAP [3-6, 9-11].

If, the physiological mechanism that leads to the development of a first VAP in general ICU population has been extensively described, the VAP relapse, that yet concern 25% of patients [18], have unfortunately not been fully addressed. The few published reports focused mainly on nonfermenting Gram-negative bacilli (GNB) and non-trauma patients [12-20]. Up-to-date, there is no data on MSSA-VAP relapse in trauma and NTBI patients.

However, given the high incidence of MSSA-VAP in trauma and NTBI patients and the negative impact of VAP on weaning from mechanical ventilation outcomes [1, 21], a better understanding of the incidence, the risk factors and the consequences of MSSA-VAP relapse on outcomes, is of high clinical importance.

We hypothesized that factors associated with MSSA-VAP relapse could be identified and that MSSA-VAP relapse was associated with longer duration of mechanical ventilation.

We thus conducted a retrospective study to measure the incidence and risk factors of MSSA-VAP relapse and analyse its relationship with mechanical ventilation withdrawal in trauma and NTBI patients who developed a first episode of MSSA-VAP.

Materials and Methods

Study design and settings

This was a monocentric retrospective study. The data were collected from adults hospitalized in a 17-bed surgical ICU from January 2009 to January 2015. The data file was declared to the French Data Protection Agency (CNIL, N° 1925005) and the study was approved by the institutional review board (IRB 00006477) of Bichat hospital, Paris 7 University, AP-HP. In accordance with the French law, written informed consent was not required. Results were reported according to guidelines (Table S1).

Patients

Any ICU trauma or NTBI patients requiring intubation and who developed a first episode of VAP documented to MSSA was considered for inclusion. Patient with history of infectious pneumonia prior to the intubation or an infection related to methicillin-resistant *Staphylococcus aureus* were not eligible. Patients discharged from the ICU during the 48h following the MSSA-VAP diagnostic were also excluded.

Definitions and follow up

According to current guidelines [1], MSSA-VAP was defined by the presence in an intubated patient of 1) a new or persistent infiltrates on chest X-ray 48 hours after intubation and mechanical ventilation 2) at least 2 of the following criteria: purulent tracheal secretions, fever greater than or equal to 38.5°C or hypothermia less than or equal to 36.5°C, leucocytosis

greater than 10^9/L or lower leukopenia, 3) a positive quantitative culture of lower respiratory tract (LRT) samples: either bronchoalveolar lavage with a threshold > 10^4 colony forming unit (cfu)/ml or either plugged telescopic catheter with a threshold > 10^3 cfu/ml, showing MSSA alone or in association with other bacteria and 4) a decision was made to initiate antibiotic therapy. Same criteria applied also for VAP related to other pathogens.

The onset of MSSA-VAP relapse was then observed during a period that extend from the first day of antibiotic therapy until either the end of ICU stay or the death in the ICU or until 28 days after the initiation of antibiotics, depending on which occurred first.

MSSA-VAP relapse was defined by new or persistent clinical, biological and radiological signs compatible with pneumonia, that conducted physicians to performed a second LRT sample, confirmed by significant growth in quantitative culture with the same thresholds as described above. MSSA-VAP relapse definitions were adapted from a recent randomized control trial [22] and included (Figure 1):

MSSA-VAP treatment failure that encompassed*:*

1. **Persistent MSSA-VAP** in case of isolation of at least MSSA in a second LRT sample performed between four days after the initiation and two days after the end of the first-line antibiotic therapy.

2. **Recurrent MSSA-VAP** in case of isolation of at least MSSA, from a second LRT samples performed two full days after the end of first-line antibiotics. The LRT sample performed during the four days after antibiotics initiation was not considered for the definition of persistent or recurrent MSSA-VAP.

Other pathogen - VAP that encompassed:

3. **Superinfection** in case of isolation of at least a pathogen other than the initial causative pathogens from LRT sample obtained at any time during the first-line antibiotic therapy.

4. **New infection** in case of isolation of at least a pathogen different from the initial causative pathogens from LRT culture obtained after completion of the first-line antibiotic therapy.

In case of both presence of MSSA and another pathogen in the second LRT sample, the patient could be classified as both, Persistent MSSA-VAP and Superinfection, or both Recurrent MSSA-VAP and New infection (Figure S1).

According to our local procedure, the decision to perform a second lower respiratory tract sample was left to the discretion of the physician in charge of the patient.

Endpoints

Our first primary endpoint was the occurrence of MSSA-VAP treatment failure defined by the presence of the criteria 1 or 2.

Our second primary outcome was the occurrence of an other pathogen-VAP defined by the presence the criteria 3 or 4.

Secondary outcome was the mechanical ventilation withdrawal across the study period (28 days).

Data collection

The following data were collected for every included patient: age, gender, main comorbidities, prehospital clinical variables (eg. Glasgow coma scale, the need for prehospital intubation), type of trauma, causes of NTBI, duration of mechanical ventilation. The microbiological characteristics of the first episode of pneumonia (cfu count of MSSA, presence and type of associated pathogens) and of the antibiotic therapy (type of antibiotics, appropriate empirical treatment regarding the antibiogram) were also collected. The Simplified Acute Physiology Score (SAPS II) and Injury Severity Score (ISS) and the presence of an acute respiratory distress syndrome (ARDS) at the time of the first MSSA-VAP diagnostic, were also recorded.

Statistical analysis

Continuous variables are expressed as median (0.25-0.75 interquartile range) and categorical variables are expressed as absolute and relative frequency. Factors associated with MSSA-VAP treatment failure and other pathogen - VAP were investigated using univariate logistic regression models, and those associated with p-value less than 0.20, or clinically relevant were proposed in a multivariate logistic regression model. Variable selection was performed using the stepwise procedure based on the Akaike criterion (both forward and backward procedures). Results were reported as adjusted Odds-ratios (OR), with their 95% confidence interval (95%CI). The performance of the models was explored using the Area under the ROC (discrimination) and the Hosmer and Lemeshow goodness of fit test (calibration). To assess the association of MSSA-VAP treatment failure, on the one hand, and other pathogen-VAP, on the other hand, with mechanical ventilation withdrawal, we performed a Landmark analysis whereby the exposure status (either treatment failure or other pathogen-VAP) is defined **before** the Landmark time point (any exposure occurring after that

time point is ignored) and the outcome of interest (end of mechanical ventilation) is measured **after** that time point (patients with the outcome of interest before that time point are excluded from the analysis). The method is suitable to account for reverse causality. We defined the Landmark time at 12 days, since the median time of each exposure was 8 and 9 days respectively, and the median duration of mechanical ventilation was 16 days in patients with VAP relapse, and 23 days in patients with no relapse. Adjusted hazard ratios of mechanical ventilation withdrawal associated with MSSA-VAP treatment failure, on the one hand, and other pathogen-VAP, on the other hand, were estimated using multivariate Cox proportional hazard models. Missing data imputation was not necessary (less than 0.1% of missing data). Analyses were performed using R version 3.6.1.

RESULTS

Characteristics of the patients

The study flowchart is represented in the figure 2. One hundred and sixty-five patients with MSSA-VAP patients were included. The characteristics of the patients are described in the table 1. Among them, 117 (71%) were admitted for trauma and 48 (29%) for NTBI. The characteristics between trauma and NTBI patients are compared in Table S2. Duration of mechanical ventilation prior to the diagnostic of MSSA-VAP first episode was 4 (3-6) days. ICU-mortality rate was 8% (n=13) and length of ICU stay was 21 (14-33) days.

MSSA-VAP relapse was observed in 54 (33%) patients. Table 1 depicts the characteristics of patients with and without MSSA-VAP relapse. Empirical antibiotic therapy appropriateness was confirmed in 158 (96%) patients and did not differ between patients with (92%) or without MSSA-VAP relapse (97%).

First primary endpoint – MSSA-VAP treatment failure

Twenty-eight (17%) patients presented an MSSA-VAP treatment failure, among them, 11 (7%) had persistent MSSA-VAP and 17 (10%) had recurrent MSSA-VAP. Univariate analysis of factors associated with MSSA-VAP treatment failure is reported in the table S3. In multivariate analysis, the presence of oropharyngeal flora (OR 3.64 95%CI 1.14 - 11.47, p=0.026) and the presence of *Streptococcus* in the initial respiratory sample (OR 7.37 95%CI 1.15 - 51.75, p=0.036) were associated with MSSA-VAP treatment failure (Table 2). More details about the variables selected, and the performance of the models are available in Supplemental (Figure S2 and S3).

Among the whole population, antibiotics were more frequently secondarily adapted into amoxicillin-clavulanic acid in patients with oropharyngeal flora or *Streptococcus* present in association with MSSA than their counterparts (63% vs. 30%, p<0.001). Same results was observed in the sub-group of the 28 MSSA-VAP treatment failure patients, with higher rate of amoxicillin-clavulanic acid use in patients with MSSA-associated oropharyngeal flora or *Streptococcus* (62% vs. 13%, p=0.016).

Second primary endpoint – other pathogen - VAP

Forty-six (28%) patients developed an other pathogen - VAP. Among them, 14 (8%) were superinfections and 32 (19%) were new infections. Univariate analysis of factors associated with other pathogen - VAP is reported in the table S4. Multivariate analysis showed that two factors were independently associated with a higher risk of other pathogen - VAP, the need for emergent surgery (OR 5.71 95%CI 1.48–37.97, p=0.027) and the presence of ARDS at the time of the first MSSA-VAP (OR 3.99 95%CI 1.53–10.83, p=0.005). One factor, the Glasgow coma score was independently associated with a lower risk of new-pathogen VAP (OR: 0.89 95%CI 0.81–0.97, p= 0.019) (Table 2).

Weaning from mechanical ventilation outcome

In the Landmark analysis no relationship could be demonstrated between MSSA-VAP relapse and duration of mechanical ventilation (Figure 3).

Discussion

To the best of our knowledge, this is the largest published study of trauma and NTBI patients with MSSA-VAP and the first that focused specifically on factors associated with its relapse.

Main results can be summarized as follows: in intubated trauma and NTBI patients, 1) MSSA-VAP relapse is frequent (on third of patients) despite appropriate empirical antibiotics, 2) MSSA-treatment failure (17% of patients) is predicted by the microbiological association with *Streptococcus* species or oropharyngeal flora, 3) other pathogen – VAP (28% of patients) is independently predicted by the severity of the disease (Glasgow coma scale, ARDS, emergent surgery) and 4) both, MSSA-VAP treatment failure and other pathogen – VAP, did not significantly prolonged the duration of mechanical ventilation.

MSSA-VAP relapse

The 33% rate of MSSA-VAP relapse observed in our study is in line with the around 30% rate observed in other population (non-surgical ICU patients) and with other pathogens such as nonfermenting GNB [12-20]. In non-surgical patients, one study reported a 14% rate of MSSA-VAP recurrence [20], which was also similar to the 10% of MSA-VAP recurrence observed in our study. Thus, VAP-relapse seems neither to depend on the type of patient (surgical or medical) or on the initial causative pathogen [12]. Moreover, the absence of association between the appropriateness of the empirical antibiotic therapy and VAP relapse has also been observed by others [14, 18, 19].

MSSA-VAP treatment failure

In this study we reported, for the first time, an independent association between the presence of *Streptococcus* species or oropharyngeal flora as co-infection and the risk of MSSA-VAP treatment failure. Permanent naso-pharyngeal carriage of MSSA is common in general population (around 20%) [23], and encountering *Streptococcus* species, oropharyngeal flora or MSSA in LRT samples, especially after brain injury, is highly suggestive of aspiration. We first hypothesized that the presence of oropharyngeal flora or *Streptococcus* reflects the volume of the aspirate, the MSSA inoculum, and thus the subsequent treatment failure. In our study, quantity of MSSA was two-fold higher in patients with MSSA-VAP treatment failure (even non significant). Moreover, the association between Glasgow coma scale and the onset of other pathogen – VAP reinforce the aspiration hypothesis (e.g. *Enterobacteriaceae* not covered by empirical antibiotics), also in line with data from similar settings, showing that neurological failure at admission is associated with the onset of MSSA-VAP [20].

Our second hypothesis is that amoxicillin-clavulanic acid, which was more frequently used in case of oropharyngeal flora or *Streptococcus* identification, was less effective than antistaphylococcal beta-lactam (e.g. oxacillin or cloxacillin) for the treatment of MSSA, even both empirical choices judged appropriate. Indeed, despite the lack of randomized control trial, it has been demonstrated in retrospective [24] and prospective [25] studies that using specific antistaphylococcal antibiotics, rather than amoxicillin-clavulanic acid or other beta-lactam-beta-lactamase, as first-line treatment of MSSA bacteraemia, was associated with higher treatment success and survival. In addition, *in vitro* data, showed that amoxicillin-clavulanic acid, was more resistant to the inoculum effect and staphylococcal beta-lactamase than other antistaphylococcal antibiotics [26]. This hypothesis may challenges the choice of

having preferred amoxicillin-clavulanic, as definitive antibiotic monotherapy, in case of oropharyngeal flora or *Streptococcus* co-infection.

Other pathogen – VAP

The main independent predictive factor of VAP relapse observed in the literature is the presence of an ARDS at the time of the first VAP diagnosis. Our results support also this finding, especially for the prediction of other pathogen – VAP. If longer duration of mechanical ventilation during ARDS could simply explain this result, other immunological explanations could be proposed. Indeed, alveolar neutrophils dysfunction during ARDS [27] may favour treatment failure or new infections. Moreover, adapting the two-hit inflammatory response model in major trauma, first hit (trauma) survivors, who underwent a second insult (e.g. ARDS), enter in an immunosuppressive state called Compensatory Anti-inflammatory Response Syndrome (CARS) [28]. This CARS is proportional to the initial inflammatory response [7] and associated with the development of secondary infection [29]. As an illustration, it has been observed that Interleukine 6 plasma level of trauma patients at admission was associated with subsequent VAP treatment failure [4].

In this study, the need for emergent surgery was also an independent predictor of other pathogen – VAP and could be explained by the fact that intraoperative prophylactic antibiotic exposure may favour the emergence of MSSA [30], and induce antibiotic resistance. In a cohort of patient with VAP caused by *Pseudomonas aeruginosa*, previous exposure to fluoroquinolone was associated with treatment failure [15].

Finally, and after adjustments on variables associated with longer duration of mechanical ventilation (e.g. SAPS 2, initial Glasgow coma scale, presence of ARDS, need for emergent surgery) no causal relationship between MSSA-VAP relapse and duration of mechanical ventilation could have been demonstrated. This could be put in parallel with the

fact that obvious reverse causality exists between MSSA-VAP relapse and duration of mechanical ventilation (one can favor the other reciprocally).

Limitations

Firstly, it was a retrospective study, which involves a potential bias in patient selection or data collection. Secondly, the lack of consensual definition of VAP-relapse in Guidelines [1] led us to establish specific definitions for our purpose adapted from those retained in recent international trial [22] and other [18, 19]. Thirdly, given the low ICU mortality rate observed in this study (8%), we decided to not analyse the association between MSSA-VAP relapse and mortality. Fourthly, we did not perform any assessment of nasal carriage of MSSA at ICU admission, which could have reinforced the aspiration hypothesis. Finally, there was no molecular typing of MSSA culture, no patient biological inflammatory response assessment and no antibiotic dosing. Thus, we could not exactly determine whether MSSA-VAP relapse observed was also eventually linked to specific patient factors (e.g. immunological response), treatment factors (e.g. appropriate antibiotics dosing), or bacterial factors (e.g. enhanced virulence).

Conclusion

Early and simply identifiable factors predict MSSA-VAP relapse and may prompt clinicians for optimized antibiotic administration and surveillance. Above all, these new findings pave the way for further studies that should clarify the pathophysiological mechanisms of MSSA-VAP relapse and may suggest to test new strategies in the choice of beta-lactam when facing MSSA-VAP associated with oropharyngeal flora or *Streptococcus species*.

Acknowledgments

No specific acknowledgments

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Tables and Figures

Table 1. Characteristics of the patients with and without methicillin sensitive staphylococcus aureus - ventilator associated pneumonia (MSSA-VAP) relapse

Variables	Whole population n = 165	MSSA-VAP relapse	
		YES n = 54	NO n = 111
Age, *years*	37 [23–53]	29 [22–49]	42 [24-55]
Gender *(male), %*	126 (76)	46 (85)	80 (72)
Comorbidities			
Chronic respiratory disease, *n (%)*	6 (4)	2 (4)	4 (4)
Arterial hypertension, *n (%)*	30 (18)	7 (13)	25 (21)
Diabetes, *n (%)*	10 (6)	1 (2)	9 (8)
Admission for trauma	**117 (71)**	**41 (76)**	**76 (68)**
Injury severity score	25 (18–29)	25 [18–29]	26 (19–41)
Injury severity score >15, *n (%)*	113 (97)	38 (93)	75 (99)
Brain trauma, *n (%)*	97 (83)	35 (85)	62 (82)
Thoracic trauma, *n (%)*	56 (48)	21 (51)	35 (46)
Abdominal and pelvic trauma, *n (%)*	44 (38)	15 (37)	29 (38)
Spine trauma, *n (%)*	39 (33)	15 (37)	24 (32)
Multiple trauma, *n (%)*	72 (62)	28 (68)	44 (58)
Admission for non-traumatic brain injury, n (%)	**48 (29)**	**13 (24)**	**35 (32)**
Subarachnoid haemorrhage, *n (%)*	22 (46)	4 (30)	18 (51)
Intraparenchymal haemorrhage, *n (%)*	19 (40)	5 (38)	14 (40)
Other, *n (%)*	7 (15)	3 (23)	4 (11)
Severity at admission			
Simplified acute physiology score 2	37 (29–51)	35 [29-51]	35 (25–48)
Acute respiratory failure, *n (%)*	26 (16)	7 (13)	19 (17)
Glasgow coma scale, *n (%)*	11 (6–14)	9 (5–14)	14 (8–15)
Need for vasopressors, *n (%)*	41 (25)	12 (22)	29 (26)
Need for prehospital intubation, *n (%)*	118 (72)	40 (74)	78 (70)
Need for emergent surgery, *n (%)*	137 (83)	52 (96)	85 (77)
Characteristics of the first MSSA-VAP			
Time between intubation and MSSA-VAP, *days*	5 (3–7)	5 (3–5)	5 (3–7)
Presence of ARDS, *n (%)*	28 (17)	16 (30)	12 (11)
Quantity of MSSA in LRT (CFU/mL)	3.10^4 (4.10^3–10^5)	3.10^4 (3.10^3–10^5)	2.10^4 (2.10^3–10^5)
Presence of other pathogens, *n (%)*	96 (58)	28 (52)	68 (61)
Streptococcus species	22 (13)	10 (19)	11 (11)
Oropharyngeal flora	22 (13)	7 (13)	15 (14)
Enterobactericeae species	30 (18)	5 (9)	25 (23)
Pseudomonas aeruginosa	9 (5)	0 (0)	9 (8)
Initial antibiotic therapy			
Amoxicillin-clavulanic acid	75 (45)	30 (56)	45 (41)
Cefepim	70 (42)	12 (43)	58 (42)
Piperacillin-tazobactam	4 (2)	0 (0)	4 (4)
Association of 2 antibiotic agents	101 (61)	30 (56)	71 (64)
Aminosid	105 (64)	34 (63)	71 (64%)

Continuous variables are expressed as median (inter-quartile range) and categorical data as n (%).
SAPS II, Simplified Acute Physiology Score II; ISS, Injury Severity Score; CGS, Coma Glasgow Score. MSSA-VAP, methicillin sensitive staphylococcus aureus – ventilator associated pneumonia

Table 2. Multivariable analysis of factors associated with methicillin sensitive staphylococcus aureus – ventilator associated pneumonia (MSSA-VAP) treatment failure and other pathogen VAP.

	Prediction model of MSSA-VAP treatment failure		**Prediction model of Other pathogen -VAP**	
Variables	OR (95%CI)	P value	OR (95%CI)	P value
Age > 40 years-old	0.98 (0.95–1.01)	0.156	-	-
Initial Glasgow coma scale	-	-	0.89 (0,81–0.97)	**0.019**
***Enterobacteriaceae* in the MSSA-VAP**	0.24 (0.03–1.01)	0.091	0.36 (0.09–1.06)	0.085
***Streptococcus* in the MSSA-VAP**	7.37 (1.15–51.75)	**0.036**	-	-
Oropharyngeal flora in the MSSA-VAP	3.64 (1.14–11.47)	**0.026**	-	-
Quantity of MSSA in the MSSA-VAP			0.99 (0.99–1)	0.299
Need for emergent surgery	10.49 (1.56–247.19)	0.052	5.71 (1.48–37,97)	**0.027**
ARDS associated with first MSSA-VAP	-	-	3.99 (1.53–10.83)	**0.005**
Prehospital shock	0.27 (0.01–1.49)	0.222	-	-

OR, odds ratio; CI, confidence interval; ARDS, acute respiratory distress syndrome

Figure 1. Definitions of methicillin sensitive staphylococcus aureus ventilator associated pneumonia (MSSA-VAP) treatment failure and Other pathogen – VAP, adapted from [22]

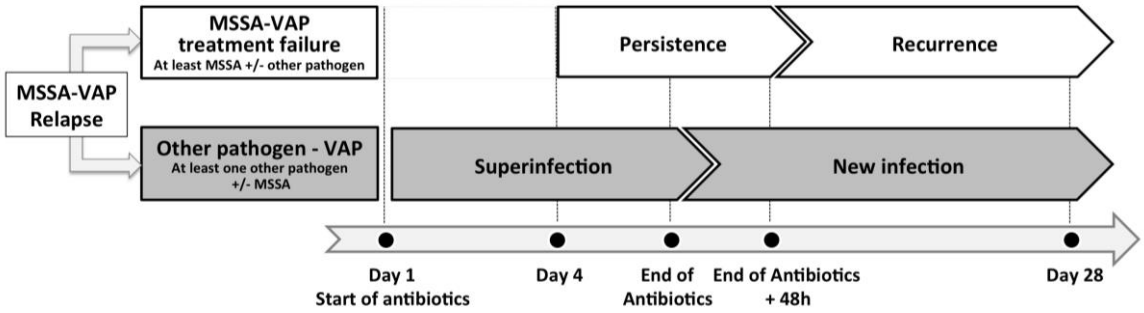


Figure 2. Study flow chart

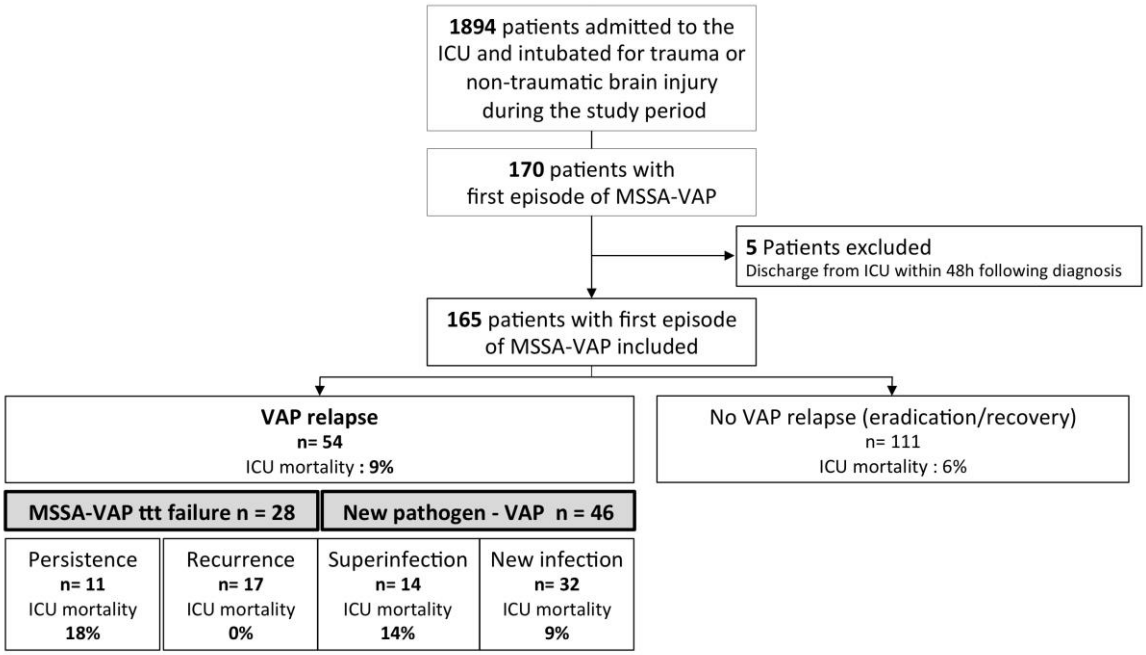
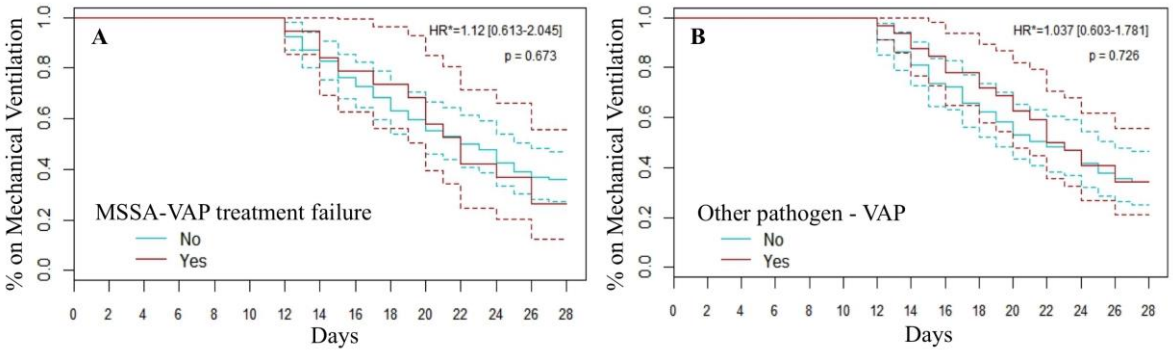


Figure 3. Figure 3. Cumulative probability of still being under mechanical ventilation according to methicillin sensitive staphylococcus aureus - ventilator associated pneumonia (MSSA-VAP) treatment failure (Panel A) and other pathogen – VAP (Panel B) using landmark analysis.



Dotted lines represent the 95% confidence intervals

* Hazard ratios are adjusted on simplified acute physiology score 2, initial Glasgow coma scale, presence of an acute respiratory distress syndrome at the time of the first MSSA-VAP and the need for emergent surgery at admission.

Prediction models of methicillin sensitive staphylococcus aureus ventilator associated pneumonia relapse in trauma and brain injury patients: a retrospective analysis

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Supplemental

Table S1. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): The TRIPOD statement

Table S2. Characteristics of patients admitted for trauma and non-traumatic brain injury

Table S3. Univariate analysis of methicillin sensitive Staphylococcus aureus - ventilator associated pneumonia (MSSA-VAP) treatment failure

Table S4. Univariate analysis of other pathogen - ventilator associated pneumonia (VAP)

Figure S1. Patients' repartition between methicillin sensitive staphylococcus aureus – ventilator associated pneumonia (MSSA-VAP) treatment failure and/or other pathogen ventilator associated pneumonia (Other pathogen-VAP).

* at significant culture threshold

Figure S2. Area under the ROC (discrimination) of the multivariate logistic regression model for the prediction of methicillin sensitive Staphylococcus aureus - ventilator associated pneumonia (MSSA-VAP) treatment failure

Figure S3. Area under the ROC (discrimination) of the multivariate logistic regression model for the prediction of other pathogen – ventilator associtaed pneumonia (other pathogen – VAP).

Table S1. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): The TRIPOD statement

Section/Topic	n	Checklist Item	Page
Title and abstract			
Title	1	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract	2	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	4
Introduction			
Background and objectives	3a	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	6
	3b	Specify the objectives, including whether the study describes the development or validation of the model or both.	6-7
Methods			
Source of data	4a	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	7
	4b	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	7-8
Participants	5a	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	7
	5b	Describe eligibility criteria for participants.	7-8
	5c	Give details of treatments received, if relevant **(antibiotics)**	10
Outcome	6a	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	10
	6b	Report any actions to blind assessment of the outcome to be predicted.	NA
Predictors	7a	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	9-10
	7b	Report any actions to blind assessment of predictors for the outcome and other predictors.	NA
Sample size	8	Explain how the study size was arrived at.	NA
Missing data	9	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	10
Statistical analysis methods	10a	Describe how predictors were handled in the analyses.	10 Fig S2/3
	10b	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	10 and Fig S2/3
	10d	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	Fig S2/3
Risk groups	11	Provide details on how risk groups were created, if done.	NA
Results			

Participants	13a	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	11 Fig 2
	13b	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	11
Model development	14a	Specify the number of participants and outcome events in each analysis.	11-12
	14b	If done, report the unadjusted association between each candidate predictor and outcome.	Table S3/S4
Model specification	15a	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	Fig S2/3
	15b	Explain how to the use the prediction model.	10 Fig S2/3
Model performance	16	Report performance measures (with CIs) for the prediction model.	Fig S2/3
Discussion			
Limitations	18	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	16
Interpretation	19b	Give an overall interpretation of the results, considering objectives, limitations, and results from similar studies, and other relevant evidence.	14-15
Implications	20	Discuss the potential clinical use of the model and implications for future research.	14-15
Other information			
Supplementary information	21	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	NA
Funding	22	Give the source of funding and the role of the funders for the present study.	NA

Table S2. Characteristics of patients admitted for trauma and non-traumatic brain injury

Variables	Reason for admission		*P-value*
	Trauma n = 117	**Non traumatic brain injury n = 48**	
Age, *years*	30 (22–49)	50 (36–59)	<0.001
Gender *(male), %*	97 (83)	29 (60)	0.002
Comorbidities			
Chronic respiratory disease, *n (%)*	4 (3)	2 (4)	0.615
Arterial hypertension, *n (%)*	11 (9)	19 (40)	<0.001
Diabetes, *n (%)*	4 (3)	10 (13)	0.064
Severity at admission			
Simplified acute physiology score 2	38 (29–52)	36 (25–50)	0.291
Acute respiratory failure, *n (%)*	25 (21)	1 (2)	0.002
Glasgow coma scale, *n (%)*	9 (6–14)	14 (9–15)	0.002
Need for vasopressors, *n (%)*	38 (32)	3 (6)	<0.001
Need for prehospital intubation, *n (%)*	96 (82)	22 (45)	<0.001
Need for emergent surgery, *n (%)*	95 (81)	42 (88)	0.327
Characteristics of the first MSSA-VAP			
Time between intubation and MSSA-VAP, *days*	5 (3–7)	5 (3–7)	0.601
Presence of ARDS, *n (%)*	20 (17)	8 (17)	0.947
Quantity of MSSA in LRT (CFU/mL)	3.10^4 (5.10^4–10^5)	3.10^4 (4.10^3–10^5)	0.812
Presence of other pathogens, *n (%)*	62 (53)	34 (71)	0.035
Streptococcus species	13 (11)	9 (19)	0.053
Oropharyngeal flora	11 (9)	11 (23)	0.020
Enterobactericeae species	22 (19)	8 (17)	0.715
Pseudomonas aeruginosa	2 (6)	1 (2)	0.641
Initial antibiotic therapy			
Amoxicillin-clavulanic acid	55 (47)	20 (42)	0.476
Cefepim	45 (38)	21 (44)	0.386
Piperacillin-tazobactam	3 (3)	1 (2)	0.725
Association of 2 antibiotic agents	78 (67)	23 (48)	0.025
Aminosid	77 (66)	28 (58)	0.364

Continuous variables are expressed as median (inter-quartile range) and categorical data as n(%). SAPS II, Simplified Acute Physiology Score II; ISS, Injury Severity Score; CGS, Coma Glasgow Score. MSSA-VAP, methicillin sensitive staphylococcus aureus – ventilator associated pneumonia; ARDS, acute respiratory distress syndrome

Table S3. Univariate analysis of methicillin sensitive Staphylococcus aureus - ventilator associated pneumonia (MSSA-VAP) treatment failure

Variables	MSSA-VAP treatment failure		*P-value*
	YES n = 28	**NO n = 137**	
Age, *years*	30 [20–46]	39 [24-54]	0.058
Gender *(male), %*	24 (86)	102 (74)	0.201
Comorbidities			
Chronic respiratory disease, *n (%)*	2 (7)	4 (3)	0.269
Arterial hypertension, *n (%)*	5 (19)	25 (18)	0.961
Diabetes, *n (%)*	1 (4)	9 (7)	1.000
Admission for trauma, *n (%)*	**18 (64)**	**99 (72)**	**0.397**
Injury severity score	25 [19–26]	25 (18–29)	0.457
Injury severity score >15, *n (%)*	17 (94)	96 (97)	0.492
Traumatic brain injury , *n (%)*	16 (89)	81 (82)	0.846
Thoracic trauma, *n (%)*	9 (50)	47 (47)	0.826
Abdominal and pelvic trauma, *n (%)*	7 (39)	37 (37)	0.789
Spine trauma, *n (%)*	8 (29)	31 (22)	0.500
Multiple trauma, *n (%)*	10 (36)	62 (45)	0.353
Admission for non-traumatic brain injury, n (%)	**10 (36)**	**38 (28)**	**0.397**
Subarachnoid haemorrhage, *n (%)*	5 (50)	17 (45)	0.512
Intraparenchymal haemorrhage, *n (%)*	4 (40)	15 (39)	0.872
Other, *n (%)*	2 (20)	5 (13)	0.348
Severity at admission			
Simplified acute physiology score 2	34 [27-48]	37 (29–51)	0.447
Acute respiratory failure, *n (%)*	5 (17)	21 (15)	0.546
Glasgow coma scale, *n (%)*	12 (7–15)	11 (6–14)	0.879
Need for vasopressors, *n (%)*	5 (18)	36 (26)	0.348
Need for prehospital intubation, *n (%)*	18 (64)	100 (73)	0.352
Need for emergent surgery, *n (%)*	27 (96)	110 (80)	0.050
Characteristics of the first MSSA-VAP			
Time between intubation and MSSA-VAP, *days*	5 (3–5)	5 (3–7)	0.135
Presence of ARDS, *n (%)*	7 (25)	21 (16)	0.266
Quantity of MSSA in LRT (CFU/mL)	4.10^4 (5.10^3–10^5)	2.10^4 (4.10^3–10^5)	0.250
Presence of other pathogens, *n (%)*	15 (53)	81 (59)	0.587
Streptococcus species	6 (21)	16 (12)	0.062
Oropharyngeal flora	7 (25)	15 (11)	0.064
Enterobactericeae species	5 (9)	25 (22)	0.591
Pseudomonas aeruginosa	0 (0)	9 (5)	0.360
Initial antibiotic therapy			
Amoxicillin-clavulanic acid	16 (57)	59 (43)	0.174
Cefepim	12 (43)	58 (42)	0.959
Piperacillin-tazobactam	0 (0)	4 (3)	0.219
Association of 2 antibiotic agents	15 (54)	86 (64)	0.362
Aminosid	18 (64)	87 (63)	0.937

Continuous variables are expressed as median (inter-quartile range) and categorical data as n(%).
SAPS II, Simplified Acute Physiology Score II. ISS, Injury Severity Score. CGS, Coma Glasgow Score. MSSA-VAP, methicillin sensitive staphylococcus aureus – ventilator associated pneumonia

Table S4. Univariate analysis of other pathogen - ventilator associated pneumonia (VAP)

Variables	Other pathogen VAP		*P-value*
	YES n = 46	**NO n = 119**	
Age, *years*	28 [22–49]	41 [24–55]	0.022
Gender *(male), %*	38 (82)	88 (74)	0.230
Comorbidities			
Chronic respiratory disease, *n (%)*	2 (4)	4 (3)	0.765
Arterial hypertension, *n (%)*	6 (13)	24 (20)	0.274
Diabetes, *n (%)*	0 (0)	10 (8)	0.865
Admission for trauma	**35 (76)**	**82 (69)**	**0.357**
Injury severity score	25 (18–29)	25 (18–29)	0.960
Injury severity score >15, *n (%)*	35 (100)	78 (95)	0.950
Traumatic brain injury, *n (%)*	30 (86)	67 (82)	0.294
Thoracic trauma, *n (%)*	17 (49)	39 (48)	0.612
Abdominal and pelvic trauma, *n (%)*	12 (34)	32 (39)	0.707
Spine trauma, *n (%)*	17 (37)	26 (32)	0.390
Multiple trauma, *n (%)*	23 (66)	49 (60)	0.307
Admission for non-traumatic brain injury, n (%)	**11 (24)**	**37 (31)**	**0.317**
Subarachnoid haemorrhage, *n (%)*	6 (60)	16 (43)	0.312
Intraparenchymal haemorrhage, *n (%)*	4 (36)	15 (41)	0.712
Other, *n (%)*	1 (9)	6 (16)	0.279
Severity at admission			
Simplified acute physiology score 2	35 (29–52)	37 (29–51)	0.737
Acute respiratory failure, *n (%)*	6 (13)	20 (17)	0.546
Glasgow coma scale, *n (%)*	9 (5–14)	12 (7–15)	0.017
Need for vasopressors, *n (%)*	11 (24)	30 (25)	0.634
Need for prehospital intubation, *n (%)*	37 (80)	81 (68)	0.106
Need for emergent surgery, *n (%)*	43 (93)	94 (79)	0.025
Characteristics of the first MSSA-VAP			
Time between intubation and MSSA-VAP, *days*	5 (3–6)	5 (3–7)	0.841
Presence of ARDS, *n (%)*	15 (33)	13 (11)	<0.001
Quantity of MSSA in LRT (CFU/mL)	2.10^4 (4.10^4–10^5)	5.10^4 (5.10^3–10^5)	0.074
Presence of other pathogens, *n (%)*	24 (52)	72 (61)	0.332
Streptococcus species	11 (24)	11 (9)	0.013
Oropharyngeal flora	3 (7)	19 (16)	0.089
Enterobactericeae species	5 (11)	25 (21)	0.115
Pseudomonas aeruginosa	2 (4)	7 (6)	0.691
Initial antibiotic therapy			
Amoxicillin-clavulanic acid	26 (56)	49 (41)	0.076
Cefepim	15 (33)	55 (46)	0.106
Piperacillin-tazobactam	0 (0)	4 (3)	0.754
Association of 2 antibiotic agents	27 (59)	74 (62)	0.782
Aminosid	29 (63)	76 (64%)	0.922

Continuous variables are expressed as median (inter-quartile range) and categorical data as n(%). SAPS II, Simplified Acute Physiology Score II. ISS, Injury Severity Score. CGS, Coma Glasgow Score. MSSA-VAP, methicillin sensitive staphylococcus aureus – ventilator associated pneumonia; ARDS, acute respiratory distress syndrome.

Figure S1. Patients' repartition between methicillin sensitive staphylococcus aureus – ventilator associated pneumonia (MSSA-VAP) treatment failure and/or other pathogen ventilator associated pneumonia (Other pathogen-VAP).

* at significant culture threshold

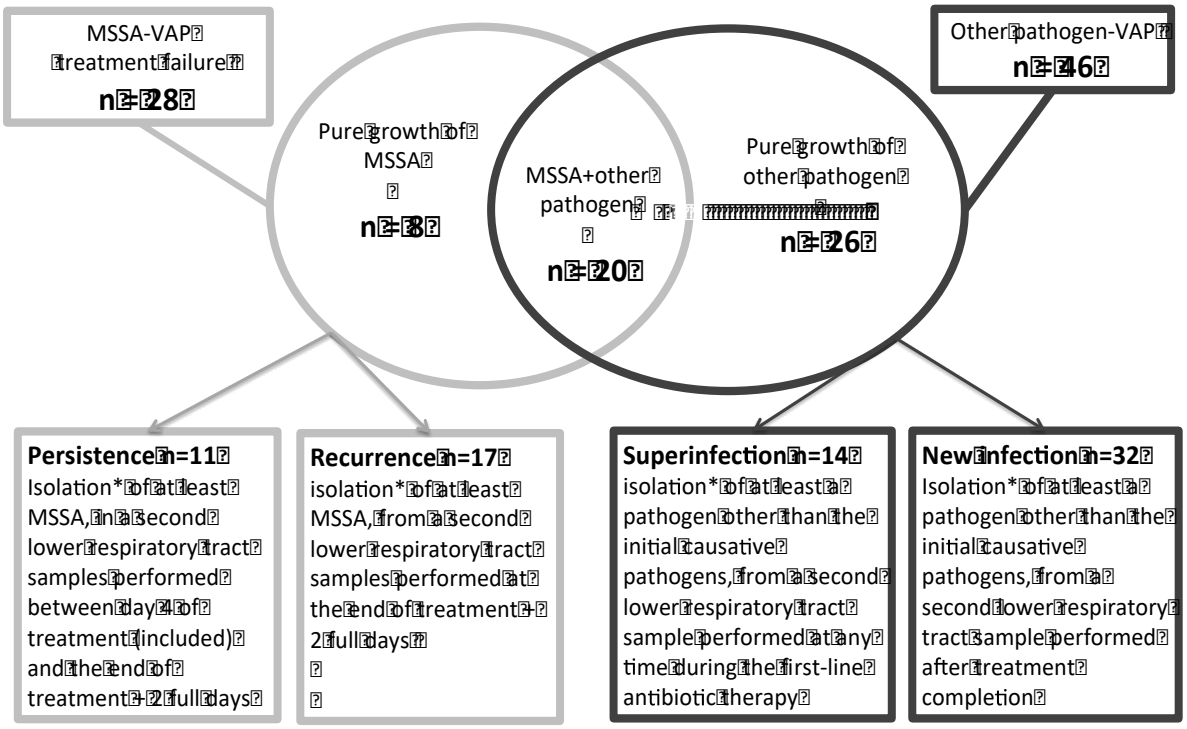
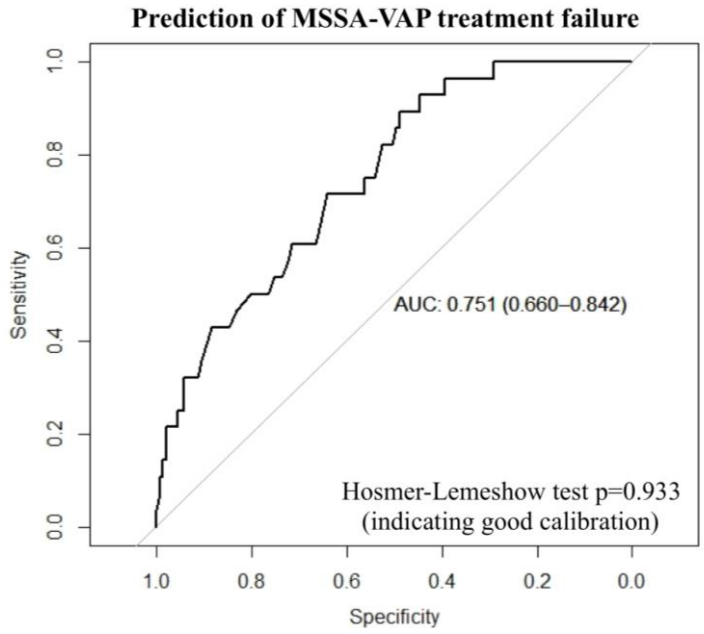
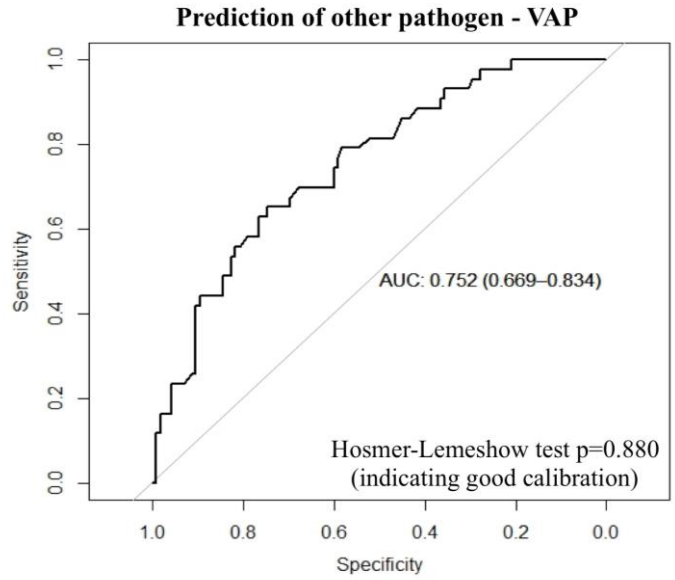


Figure S2. Area under the ROC (discrimination) of the multivariate logistic regression model for the prediction of methicillin sensitive Staphylococcus aureus - ventilator associated pneumonia (MSSA-VAP) treatment failure



For the prediction model of MSSA-VAP treatment failure the following seven variables: Age > 40 years-old / Gender / Enterobacteriaceae in the first MSSA-VAP / Oropharyngeal flora in the first MSSA-VAP / Prehospital shock / Need for emergent surgery / Streptococcus in the MSSA-VAP were proposed to the stepwise model. Then, variables were selected according to the best AIC criterion. Thus, final stepwise model retained the following variables as reported in the Table 2: Age > 40 years-old / Enterobacteriaceae in the first MSSA-VAP / Oropharyngeal flora in the first MSSA-VAP / Prehospital shock / Need for emergent surgery / Streptococcus in the MSSA-VAP.

Figure S3. Area under the ROC (discrimination) of the multivariate logistic regression model for the prediction of other pathogen – ventilator associtaed pneumonia (other pathogen – VAP).



For the prediction model of other pathogen - VAP the following eight variables: Age > 40 years-old / Initial Glasgow coma scale / Enterobacteriaceae in the first MSSA-VAP / Oropharyngeal flora in the first MSSA-VAP / Prehospital shock / Need for emergent surgery / Quantity of MSSA in the MSSA-VAP / Empirical first-line antibiotic therapy with amoxicillin-clavulanic acid were proposed to the stepwise model. Then, variables were selected according to the best AIC criterion. Thus, final stepwise model retained the following variables as reported in the Table 2: Initial Glasgow coma scale / Enterobacteriaceae in the first MSSA-VAP / Prehospital shock / Need for emergent surgery / Quantity of MSSA in the MSSA-VAP.