Ventilator-associated Pneumonia Due to MRSA vs MSSA: What Should Guide Empiric Therapy?

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Abstract

The guidelines on ventilator-associated pneumonia (VAP) recommend an empiric therapy against methicillin-resistant *Staphylococcus aureus* (MRSA) according to its prevalence rate. Considering the MRSA and MSSA VAP prevalence over the last 9 years in our tertiary care Hospital, we firstly compared patients with MRSA VAP to those with MSSA VAP in terms of length of stay (LOS) in intensive care unit (ICU) and mortality and secondly, we assessed the clinical value of the MRSA nasal-swab screening in either predicting or ruling out MRSA VAP. We extracted the data of 1461 patients with positive bronchoalveolar lavage (BAL). Regarding the MRSA nasal-swab screening, 170 patients were positive for MRSA or MSSA. Overall, MRSA had a high prevalence in our ICU. Despite the COVID pandemic, there was a significant downward trend in MRSA prevalence, while MSSA remained steady over time. Having VAP due to MRSA did not have any impact on LOS and mortality. Finally, the MRSA nasal-swab testing demonstrated a very high negative predictive value for MRSA VAP. Our results suggested the potential value of a patient-centered approach to improve antibiotic stewardship.

Introduction

Ventilator-associated pneumonia (VAP) is still one of the most frequent infections in the Intensive Care Unit (ICU) setting[1], and its attributable mortality is notoriously high[2].

Microbiological confirmation of infection is strongly encouraged, but we are frequently faced with starting an empiric therapy, since delaying treatment is associated with higher mortality rates[3]. On the other hand, if there is any uncertainty about the necessity of narrowing a broad-spectrum antibiotic therapy once the susceptibility pattern of the isolated pathogens is available, some flaws remain in the initial selection of the antimicrobial regimen[4]. For example, the awareness of local resistance patterns should be one of the cornerstones for starting an appropriate empiric therapy [5], but there is a paucity of real-life data supporting it.

Particularly, while the guidelines recommend an empiric therapy against methicillin-resistant *Staphylococcus aureus* (MRSA) rather than methicillin-susceptible *Staphylococcus aureus* (MSSA) if more than 20% of the *Staphylococcus aureus* isolates in the local ICU are MRSA[6], the real need of this choice has been poorly verified. In line with a currently prevailing mindset, we may require an individual-based approach for VAP rather than a primarily prevalence-based approach [7]. Particularly, we may be looking for more targeted risk factors for MRSA infection [8].

With this in mind, the primary aim of this study is to evaluate MRSA and MSSA VAP prevalence over the last nine years in our Hospital, Fondazione IRCCS Policlinico San Matteo of Pavia (IRCCS-FPSMP). Secondary aims are to compare patients with MRSA VAP to those with MSSA VAP in terms of length of stay (LOS) in intensive care unit (ICU) and mortality and to assess the clinical value of the MRSA nasal-swab screening, in either predicting or conversely ruling out MRSA VAP.

Results

Overall, data about 1461 positive BAL samples were extracted. Among these, 170 (11,6%) were positive for MRSA or MSSA.

Characteristics of patients with MSSA and MRSA VAP are shown in Table 1. Significantly, there was not differences in ICU between patients with MSSA and MRSA VAP.

Table 1
Characteristics of patients with MSSA and MRSA VAP.

Variables	Overall (N = 170)	MRSA (N = 41) - statistics	MSSA (N = 129) - statistics	p-value
Age (y), median (IQR)	61 (50-72.75)	66 (57-76)	60 (50-70)	0.107
Gender (male), n (%)	114 (67.1%)	26 (63.4%)	88 (68.2%)	0.705
ICU-LOS before VAP onset (days), median (IQR)	3 (0-8)	3 (0-11)	3 (0-6)	0.314
ICU LOS after VAP onset (days), median (IQR)	11 (4-26)	13 (5-23)	11 (4-27)	0.806
Polymicrobial infection, n (%)	81 (47.6%)	16 (39%)	65 (50.4%)	0.276
No. polymicrobial infection, median (IQR)	1 (1-2)	1 (1-2)	2 (1-2)	0.267
Nasal swab (screening MRSA), n (%)	95 (55.9%)	23 (56.1%)	72 (55.8%)	1,000
MRSA in nasal swab, n (%), [N = 95]	8 (8.4%)	8 (34.8%)	0 (0%)	0,000
MRSA in blood culture, n (%)	9 (5.3%)	7 (17.1%)	2 (1.6%)	0.001
MSSA in blood culture, n (%)	14 (8.2%)	0 (0%)	14 (10.9%)	0.023
P-values by Chi-squared test or Fisher's Exact test as appropriate for qualitative variables, by t-test or Mann-Whitney test as appropriate for quantitative variables. ICU: intensive care unit. IQR: interquartile range. LOS: length of stay. MRSA: methicillin-resistant <i>Staphylococcus aureus</i> . MSSA: methicillin-susceptible <i>Staphylococcus aureus</i> . VAP: ventilator-associated pneumonia.				

Among VAP due to *Staphylococcus* spp., the prevalence of MSSA significantly increased over the years from 56.5% in 2012 to 85% in 2021, by contrast the prevalence of MRSA significantly decreased from 43.5% in 2012 to 15% in 2021 ($p = 0.038$; Fig. 1). However, MRSA had a very high prevalence overall (24.1%). During the considered period of time, the prevalence of MRSA was higher than 10–20%, that is the guidelines threshold to define a low-risk ICU for VAP due to this bacterium, or slightly lower, as it

happened in 2019 (18.2%) and in the current year (15%). Exceptions are 2013 and 2017, when prevalences were significantly lower than in the other years (10% and 6.7%, respectively).

Moreover, there was a general downward trend in MRSA prevalence (from 9.4% in 2012 to 1.3% in 2021, $p = 0.001$; Fig. 2, Panel A), while MSSA remained steady over time (from 12.3% in 2021 to 7.1% in 2021, $p = 0.218$; Fig. 2, Panel B). Particularly, these trends were unaffected by the COVID pandemic.

With regard to the secondary outcomes, having a VAP due to MRSA did not have any impact on LOS ($p = 0.754$), and mortality ($p = 0.447$) (Fig. 3, Panel A and B).

Among the 1461 patients with VAP, 976 (66,8%) were tested for MRSA nasal colonisation before BAL. Accordingly with the fact that the nasal screening for MRSA was not routinely performed before 2016, the majority of the nasal tests, namely 896, were collected from 2016 on. Among the specimens collected from 2016 on, only 22 resulted positive for MRSA (2.46%) (Table 2).

Table 2
MRSA nasal-swab screening.

MRSA nasal-swab screening	Non-MRSA VAP	MRSA VAP	Total
Negative	863	11	874
Positive	14	8	22
Total	877	19	896
BAL: bronchoalveolar lavage. MRSA: methicillin-resistant <i>Staphylococcus aureus</i> . VAP: ventilator-associated pneumonia.			

The MRSA nasal swab testing demonstrated a 42.1% sensibility and 98.4% specificity, with a PPV of 36.4% and a NPV of 98.7% (Table 3).

Table 3
Statistical analysis.

Sensitivity, %	42.1
Specificity, %	98.4
PPV, %	36.4
NPV, %	98.7
NPV: negative predictive value. PPV: positive predictive value.	

Discussion

Our results showed that, despite a downward trend in prevalence of VAP due to MRSA over the last nine years, it has overall remained above 20% in the ICU of IRCCS-FPSMP.

These findings are in line with the ECDC reports, which include countries with both low and high percentages of MRSA and outline a decreasing trend of MRSA infections during the period 2015–2018 [9]. In our case, this trend was notably unaffected by the COVID pandemic. This result is not entirely concordant with the current state of the literature, since the hard COVID-19 knock on our health systems widely increased Hospital-acquired infection rates, including MRSA-related infections[10]. However, there are also some well-known and positive consequences of the measures of control and prevention implemented during the pandemic, especially on a microorganism which resides in the nose and on the skin, always covered by masks and gowns [11].

As regards the impact on the patients' outcome, MRSA did not have any effect on LOS ($p = 0.754$), and in-hospital mortality ($p = 0.447$). Differently, several studies demonstrated the association between MRSA pneumonia and both increased mortality [12] and prolonged duration of ICU LOS [13]. On the other hand, a systematic review by Athanassa and colleagues has shown the significant challenges in estimating the impact of methicillin resistance on mortality[14], especially in the absence of antibiotic treatment and severity data to estimate attributable mortality.

MRSA is indeed responsible for only a few numbers of VAP, frequently resulting in many unnecessary empiric treatments. MSSA remains more involved in VAP, which warrants greater consideration [15].

In light of the very low absolute prevalence of MRSA as a cause of VAP in our reality and the disproportionate number of patients that would need to be treated unnecessarily empirically, we would really rethink the appropriateness of using the threshold proposed by the guidelines (10–20% relative prevalence of MRSA) [16].

Instead, it might be more meaningful to consider each patient's individual risk factors for MRSA infection such as nasal colonization, previous antibiotic treatment and prolonged hospital stay, as prompted by recent findings [7]. In our opinion, this individual-based approach might be valuable also in a context where novel multiplex real-time PCR assays on respiratory materials will have a growing role in early diagnosis of VAP[17].

We want to highlight that MRSA nasal colonization, which is a recognized risk factor for MRSA VAP [20], has a significantly high NPV in our analysis. This finding brings compelling thoughts in terms of antimicrobial stewardship, as a negative MRSA nasal swab may be used to rule out MRSA VAP, and consequently guide clinicians' decisions on empirical treatment.

The limits of this study are the monocentric and retrospective nature, the lack of data on antibiotic treatments performed, and the clinical comorbidities, which are unfortunately not fully available from the ICD-9CM codes.

In conclusion, our results showed that the trend of MRSA VAP in our ICU has declined over the years, despite the COVID pandemic. Furthermore, we suggested the potential value of a patient-centered approach in order to improve antibiotic stewardship.

Methods

Study Design and participants

This is a single center, retrospective, observational cohort study.

The SkyNet database is a Relational Database Management System (RDBMS) which includes microbiological and clinical data from all the patients admitted to IRCSS-FPSMP, updated daily.

Data of positive bronchoalveolar lavage (BAL) samples of patients admitted to the ICU from 1st January 2012 to 13rd December 2021 were retrospectively extracted from the SkyNet database.

According to the new National Healthcare Safety Network (NHSN) definition [18], only the BAL from patients with imaging test results, signs and symptoms consistent with pneumonia were included.

The samples of the MRSA nasal swab testing of ICU patients with VAP from 1st January 2012 to 13rd December 2021 were retrospectively extracted from the SkyNet database. Any patient with at least one positive nasal swab for MRSA at any time before VAP onset, was considered colonized by MRSA. MRSA nasal swab screening was extensively performed on all new ICU admissions from 2016, so only data from that date onwards were considered in our statistical analysis.

Outcomes

The primary outcome was to evaluate MRSA and MSSA VAP prevalence over the last nine years in our tertiary care Hospital. The secondary outcomes were: to compare patients with MRSA VAP to those with MSSA VAP in terms of LOS and in-hospital mortality; to evaluate the performance of the MRSA nasal swab in predicting or ruling out MRSA VAP.

Accordance statment

The study protocol was written in accordance with the ethical guidelines of the 1975 Declaration of Helsinki.

Approval statment

The SkyNet Database was approved by the local Ethical Committee (Comitato Etico Pavia, n° prot. 20210068914).

All participants have signed an informed consent for data collection.

Statistical methods

The trend of positive BAL for MRSA or MSSA over the years and the differences in prevalence were evaluated by Chi-square tests for trend, while the impact on LOS and in-hospital mortality by Chi-squared test or Fisher's Exact test as appropriate. Hospitalizations were stratified as follows: LOS $\leq$ the average LOS (ALOS) and LOS > ALOS. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the MRSA nasal swab were calculated.

Declarations

Author contributions

M.C. and D.D.C. conceived the presented idea, analyzed the results and wrote the final manuscript. A.A., L.N.M., C.B., A.D.M., P.S. and F.M. encouraged to investigate and supervised the findings of this work. M.C., G.P., P.C. and A.M. contributed to the design and implementation of the research, and R.B. contributed to the final version of the manuscript and supervised the project. All authors have read and agreed to the published version of the manuscript.

Data availability statement

Raw data were generated at *SkyNet* database. Derived data supporting the findings of this study are available from the corresponding author (M.C.) on request.

Competing interests

The authors declare no competing interests.

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Figures

Figure 1

Prevalence of MRSA/MSSA in patients with VAP in ICU.

P-value by Chi-squared test for trend in proportions. ICU: intensive care unit. MRSA/MSSA: methicillin-resistant *Staphylococcus aureus*/methicillin-susceptible *Staphylococcus aureus*. VAP: ventilator-associated pneumonia.

Figure 2

Panel A: Prevalence of MRSA in patients with VAP in ICU. **Panel B:** Prevalence of MSSA in patients with VAP in ICU.

P-value by Chi-squared test for trend in proportions. ICU: intensive care unit. MRSA: methicillin-resistant *Staphylococcus aureus*. MSSA: methicillin-susceptible *Staphylococcus aureus*. VAP: ventilator-associated pneumonia.

A

B

Figure 3

Panel A: Impact of MRSA/MSSA on the length of stay in patients with VAP in ICU. **Panel B:** Impact of MRSA/MSSA on the in-hospital mortality in patients with VAP in ICU.

P-value by Pearson's Chi-squared test with Yates' continuity correction. ALOS=39 days. ALOS: average LOS. ICU: intensive care unit. LOS: length of stay. MRSA/MSSA: methicillin-resistant *Staphylococcus aureus*/methicillin-susceptible *Staphylococcus aureus*. VAP: ventilator-associated pneumonia.