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Évaluation des facteurs de risques d'échecs thérapeutiques dans le traitement des pneumopathies acquises sous ventilation mécanique à *Staphylococcus Aureus* sensible à la méticilline : étude rétrospective de 2017 à 2023 dans une réanimation polyvalente

Bastien Lemoigne

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Faculté des sciences
médicales et paramédicales
Aix-Marseille Université

Evaluation des facteurs de risques d'échecs thérapeutiques dans le traitement des pneumopathies acquises sous ventilation mécanique à *Staphylococcus Aureus* sensible à la méticilline : étude rétrospective de 2017 à 2023 dans une réanimation polyvalente

T H È S E A R T I C L E

Présentée et publiquement soutenue devant

LA FACULTÉ DES SCIENCES MÉDICALES ET PARAMÉDICALES

DE MARSEILLE

Le 6 Juin 2023

Par Monsieur Bastien LEMOIGNE

Né le 18 octobre 1995 à Évry-Courcouronnes (91)

Pour obtenir le grade de Docteur en Médecine

D.E.S. d' ANESTHÉSIE RÉANIMATION

Membres du Jury de la Thèse :

Monsieur le Professeur LEONE Marc

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Monsieur le Professeur GAINNIER Marc

Assesseur

Madame le Docteur BICHON Amandine

Directeur

Monsieur le Docteur (MCU-PH) DUBOURG Grégory

Assesseur



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2010

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2011

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| M. le Professeur | MARTIN Pierre | 31/08/2015 |
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| M. le Professeur | HENRY Jean-François | 31/08/2016 |
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I/ INTRODUCTION

La pneumonie associée à la ventilation mécanique (PAVM) est l'une des infections les plus fréquentes acquises en unité de soins intensifs/réanimation chez les patients exposés à la ventilation mécanique pendant au moins 48 heures. Son incidence varie de 5 à 40 %. La mortalité imputable aux PAVM représente entre 10 et 50% des décès en unité de soins intensifs.

D'un point de vue microbiologique, selon les dernières études épidémiologiques du centre de lutte contre les infections nosocomiales (CLIN) environ 12 % des PAVM sont causées par *Staphylococcus aureus* sensible à la méticilline (SASM) dans les USI européennes derrière le streptocoque pneumoniae. Cette prédominance pouvant atteindre 25 % dans le contexte d'une infection à la COVID-19 et/ou d'une lésion cérébrale traumatique.

Les recommandations actuelles pour la prise en charge de la PAVM à SASM avérée préconisent l'utilisation d'une pénicilline anti staphylococcique comme la cloxacilline (famille des pénicillines M) ou de céfazoline pendant au moins sept jours.

Nous avons voulu faire cette étude pour plusieurs raisons. Premièrement, les ruptures de stock récurrentes de Cloxacilline (pénicilline M commercialisée en France) ont entraîné une utilisation croissante de la céfazoline alternative recommandée par les différentes sociétés savantes françaises.

Deuxièmement, par rapport à la céfazoline, les pénicillines M étaient associées à des taux significativement plus élevés d'événements indésirables conduisant à leur interruption.

De plus, l'hypothèse de l'infériorité de la céfazoline par rapport à la pénicilline M retrouvée in vitro en raison d'une hydrolyse de la céfazoline induite par une bêta-lactamase entraînant un effet d'inoculum est contestée. La céfazoline pour les infections à SASM était associée à une mortalité globale plus faible et à moins d'échecs cliniques que les pénicillines M chez les patients en USI pour les

bactériémies ou les infections profonde non neuroméningé. Les données pharmacocinétiques et de diffusion pulmonaire étaient également en faveur de l'utilisation de la céfazoline, car les cibles plasmatiques thérapeutiques étaient atteintes plus rapidement qu'avec les pénicillines M.

Dernier argument avancé celui du coût global, le prix du traitement antibiotique était de 2 à 3 fois plus élevé lors de l'utilisation des pénicillines M par rapport à la céfazoline.

Cette étude visait à identifier les facteurs de risques indépendants associés à l'échec du traitement de la pneumonie associée à la ventilation mécanique causée par *Staphylococcus aureus* sensible à la méticilline en soins intensifs. Nous avons émis l'hypothèse que la cloxacilline était associée à des risques plus élevés d'échec du traitement par rapport à la céfazoline.

II/ Thèse

ABSTRACT

Introduction

Ventilator-associated pneumonia (VAP) are frequent and lethal in the intensive care unit (ICU). Up to a quarter of these VAP are caused by methicillin-susceptible *Staphylococcus aureus* (MSSA). Antistaphylococcal penicillin (ASP) is the recommended first-line treatment for MSSA VAP although it is frequently unavailable due to stock-outs, associated with high rates of adverse events (AEs), and controversial regarding its efficacy on MSSA infections compared with cefazolin in the recent literature. In this study, we aimed to identify the risk factors of MSSA VAP treatment failure.

Methods

We performed a monocentric study in a French polyvalent ICU over a 6-year-long period (2017-2023). Patients with a MSSA-documented VAP were retrospectively included. (#PADS22-351).

Results

131 patients were finally included. Motives of admission encompassed COVID-19 induced ARDS, cerebrovascular events, traumatic brain injury, cardiac arrest, ARDS from other cause than COVID-19 infection, and septic shock. Older age ($p = 0.029$), higher number of comorbidities (Charlson score, $p = 0.018$) and fungal co-infection (pulmonary invasive aspergillosis, $p = 0.015$) were associated with a greater risk of treatment failure in univariate analysis. In multivariate analysis, patients with concomitant bacteremia associated with MSSA VAP were more likely to present therapeutic failure (OR = 3.83, 95% CI 1.011 – 32.2, $p = 0.048$). Female gender (OR = 0.327, 95% CI 0.1 – 0.713, $p = 0.008$) and cefazolin treatment (OR = 0.3 95% CI 0.042-0.86 $p = 0.030$) were protective factors for treatment failure. Cefazolin was associated with fewer AEs (4.8% versus 10.6%, $p = 0.66$) and no serious AE was reported with cefazolin contrarily to cloxacillin.

Conclusion

In ICU, cefazolin appears to be safe and effective in the treatment of MSSA VAP even if randomized controlled-trials are therefore necessary.

RESUME EN FRANCAIS

Contexte : Les pneumonies acquises sous ventilation mécanique (PAVM) sont fréquentes et associées à une morbi-mortalité importante chez les patients de réanimation sous ventilation mécanique invasive pendant plus de 48 heures. Parmi les PAVM documentées, le *Staphylococcus aureus* méticilline-sensible (SAMS) est responsable de 10 à 25% des PAVM. Les pénicillines antistaphylococciques (PAS) constituent le traitement de première intention de ces PAVM à SAMS malgré leur indisponibilité fréquente due à des ruptures de stock, leurs multiples effets indésirables (EIs) et leur efficacité récemment controversée en comparaison avec la céfazoline (céphalosporine de première génération). **Méthode :** Afin de déterminer les facteurs de risque d'échec thérapeutique des PAVM à SAMS, nous avons mené une étude rétrospective monocentrique dans une réanimation polyvalente française sur une période de 6 ans.

Résultats : Parmi une cohorte de 131 patients, les facteurs tels que l'âge plus avancé (p 0.029), un score de fragilité plus élevé (index de Charlson, p 0.018), et la présence d'une co-infection fongique (aspergillose pulmonaire invasive p 0.015) étaient associés à l'échec thérapeutique des PAVM à SAMS. De même, une bactériémie concomitante de la PAVM était indépendamment associée à l'échec thérapeutique (OR 3.83, 95% CI 1.011 – 32.2, p 0.048). A contrario, le sexe féminin (OR: 0.327, 95% CI 0.1 – 0.713, p 0.008) et le traitement par céfazoline (OR 0.3 95%CI 0.042-0.86 p 0.030) constituaient des facteurs protecteurs contre l'échec thérapeutique. De plus, la céfazoline était associée à une tendance à la diminution des EIs (4.8% versus 10.6%, p 0.66) par rapport à la cloxacilline (PAS) ainsi qu'à moins de rechute/récidive de PAVM à SAMS (9.5% versus 23%, p 0.316).

Conclusion : Dans cette étude et de manière congruente avec la littérature, l'âge, le sexe masculin, et les bactériémies étaient indépendamment associés au risque d'échec thérapeutique des PAVM à SAMS. Le traitement par céfazoline était indépendamment associé au succès thérapeutique et était mieux toléré que la cloxacilline.

INTRODUCTION

Ventilator-associated pneumonia (VAP) is one of the most frequent intensive care unit (ICU)-acquired infection in patients exposed to invasive mechanical ventilation (IMV) for at least 48 hours. Its incidence varies from 5 to 40% and 10 to 50% of casualties in ICU are attributable to VAP.¹ Microbiologically, about 12% of VAP are caused by methicillin-susceptible *Staphylococcus aureus* (MSSA)² in European ICUs, reaching 25%³ in context of COVID-19 infection and traumatic brain injury (TBI).^{4,5} Current recommendations for proven MSSA VAP management preconize the use of an antistaphylococcal penicillin (ASP) (oxacillin, nafcillin, flucloxacillin) or cefazolin (a first generation cephalosporin effective against MSSA infection) for at least seven days.⁶ The rationale of this study encompass the following reasons. First, recurrent stock-outs of ASPs led to an increasing use of cefazolin as recommended.⁷ Second, when compared to cefazolin, ASPs were associated with significantly higher rates of adverse events (*i.e.*: renal failure, cytopenia, hepatopathy, interstitial nephritis) leading to its discontinuation.⁸ Besides, the hypothetical inferiority of cefazolin compared to penicillin M due to a beta-lactamase-induced cefazolin hydrolyzation leading to an inoculum effect was recently invalidated.⁹ Cefazolin for MSSA infection was associated with lower overall mortality and clinical failures than ASPs in ICU patients.^{8,10-13} Pharmacokinetics was also in favor of cefazolin use as therapeutic plasmatic targets were faster achieved than with ASPs.¹⁴ Finally, the overall cost of the antibiotic course was 2 to 3 times higher when using ASP compared with cefazolin.¹⁵

This study sought to identify independent risk factors associated with treatment failure of methicillin-susceptible *Staphylococcus aureus* ventilator-associated pneumonia in critical care. We hypothesized that cloxacillin was associated with higher risks of treatment failure compared to cefazolin.

METHODS

We performed a single-center retrospective study in our intensive care unit (ICU) at the Timone University Hospital in Marseille, France from January first of 2017 to January first of 2023. Our 21-bed ICU is a trauma center and is specifically affiliated for traumatic brain injury, stroke, cardiac arrests (refractory or not) and drug poisoning. From 2020 to 2022, a total of 404 patients infected with SARS-CoV-2 were admitted to our ICU for acute respiratory failure. Selective digestive decontamination is not used in our ICU as its utility in ventilated patients remains controversial¹⁶. Patients in our ICU display a 4.6-day mean length of stay with a 47-median

“index de gravité simplifié II”¹⁷(IGS II, French equivalent of “new simplified acute physiology score”¹⁷ (SAPS II)). Approximately 1500 patients per year are admitted.

All adult patients admitted in the ICU, regardless the underlying motive of admission, diagnosed during their stay with Methicillin-susceptible *Staphylococcus aureus* (MSSA) infection were screened. Only those diagnosed with proven MSSA ventilator-associated pneumonia (VAP)¹⁸ according to the Infectious Diseases Society of America (IDSA) definition⁶, leading or not to acute respiratory distress syndrome (ARDS)¹⁹, were included. This cohort was obtained from the CLIN (Comité de lutte contre les infections nosocomiales)²⁰ microbiological database (whose mission is to collect and gather all in-hospital microbiological events regardless their pathogenicity) on bronchoalveolar lavage (BAL) and/or protected specimen brush (PSB) and/or endotracheal aspirate (ETA). Both point-of-care-PCR-testing method (POC-PCR)²¹ and cultures were considered. This retrospective, monocentric, and non-interventional study was communicated to the Commission on Data Processing and Freedom and approved by the Assistance Publique des Hôpitaux de Marseille (APHM) ethics committee (approval number #PADS22-351) under French laws (MR-004 methodology that does not require the patients written consent according to French laws).²²

Exclusion criteria encompassed the absence of IMV, infection diagnosed prior to IMV, MSSA pulmonary colonization, post-mortem MSSA-induced VAP diagnosis, MRSA-induced VAP, para-pneumonic effusions, pulmonary abscesses, other site of staphylococcal infection without VAP and infections (VAP or not) documented with *Staphylococcus non-aureus* (other staphylococcal species).

Demographic and medical information was collected using computerized hospital reports, biology, imaging and pharmaceutical prescriptions. Relevant underlying conditions included cardiovascular risk factors (age > 50 years for males and > 60 years for females, high blood pressure, type 2 diabetes, hypercholesterolemia with low-density cholesterol levels > 4.1mmol/L and tobacco use)²³ and/or immunosuppression / immunomodulation (organ transplant, stem cell transplant, ongoing neoplasia / hematological malignancy, systemic disease with long-term corticosteroids, chronic kidney disease)²⁴ and a comorbidity score at admission was provided according to the Charlson Index.²⁵ Patients severity at admission was calculated based on specific ICU severity scores : IGS II¹⁷, and the sepsis-related organ failure assessment (SOFA) score.²⁶

VAP was defined by a pneumonia occurring > 48 hours after endotracheal intubation.⁶ Regarding the collection of microbiological data, systematic screening by endotracheal aspirate (ETA) on mechanically ventilated patients occurred every Monday in our ICU apart from microbiological samples performed in a context of fever or suggestive infection. Screening for multidrug-resistant carriage in mechanically ventilated patients included weekly (Mondays) swabs of the nostrils, rectum and ETA. As recommended, our laboratory (IHU Méditerranée Infection, Marseille, France) provided semiquantitative results for invasive (BAL and/or PSB) and noninvasive (ETA) samples. Positivity of those latter was established for thresholds $\geq 10^3$ CFU/mL for PSB, $\geq 10^4$ CFU/mL for BAL and $\geq 10^5$ CFU/mL for ETA.⁶ Worsening gas exchange was considered when a medical intervention was required due to clinical aggravation (*i.e.*: change of the ventilatory mode, increased level of sedation, addition of neuromuscular blockade, use of rescue therapy such as prone positioning, inhaled nitric oxide, and/or implementation of venovenous extracorporeal membrane oxygenation – VV ECMO –).

The overall population was studied. The initial probabilistic course of antibiotic for VAP was then adjusted to the proper targeted antimicrobial for proven MSSA VAP. Thus, patients were clustered according to the administered MSSA-targeted antimicrobial course: cefazolin (6g/24h), cloxacillin (12g/24h), association of penicillin A with a β -lactam inhibitor (amoxicillin-clavulanate – 6g/24h – or piperacillin-tazobactam – 16g/24h –), third or fourth generation cephalosporin (3GC/4GC) and penems. All these antibiotic courses were combined or not with aminoglycosides (amikacin 30mg/kg/day or gentamicin 10mg/kg/day) administered either intravenously or less frequently nebulized. Treatment failure was established according to a composite criteria encompassing clinical (absence of significant clinical improvement – *i.e.*: fever drop, IMV weaning with either ventilation mode change from volume controlled mode towards pressure support / spontaneous breathing trial or endotracheal extubation, significant weaning of inspired fraction of oxygen, IMV duration, respiratory-linked death –) and microbiological items (absence of pathogen clearance / colonization or persistent/recurrent VAP). Plasmatic dosing of antibiotics were performed at least once during treatment and were considered satisfactory when greater than eight times the minimum inhibitory concentration ($8 \times \text{MIC}$), or within the EUCAST epidemiological cutoff values (ECOFF)²⁷, and when the values did not exceed the upper ranges (therefore, associated with possible adverse events – AEs).

Primary endpoint included the identification of independent risk factors of treatment failure in the overall population and in subgroups of treatment. The secondary endpoint compared the occurrence of antimicrobial-induced AEs²⁸ according to the administered treatment.

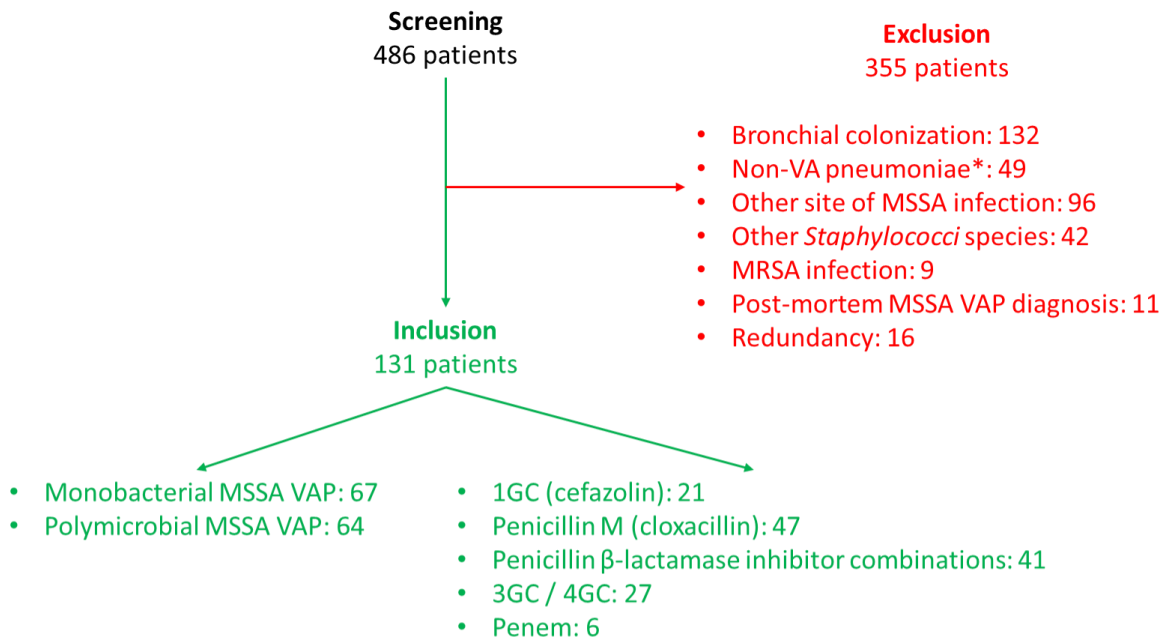
Quantitative variables were described using medians, with the 25 and 75% interquartile ranges (IQR 25–75%), and qualitative variables using frequencies and percentages. After describing the overall population, we compared populations according to their antimicrobial course using the Chi2 test (or Fisher exact test) for qualitative variables and t-test (or Mann-Whitney test) for quantitative variables. Risk factors of treatment failure were analyzed using univariate and multivariate Firth's logistic regression to minimize the analytical bias caused by small samples. A 0.05 alpha threshold of significance in univariate analysis was set. Significant parameters of treatment failure in univariate analysis with a p threshold of 0.05 were retained for the multivariate analysis, respecting the ratio of 1 variable for 10 events. The Hosmer-Lemeshow test was then used to evaluate the goodness of fit of the model. All statistical analyses were performed using SAS 9.4 software. A $p < 0.05$ was considered significant.

RESULTS

Patient characteristics

As shown in **Figure 1**, 486 ICU patients with a MSSA-positive sample were screened. We excluded 132 patients for bronchial colonization, 49 for pneumonia not related to invasive mechanical ventilation (IMV) or diagnosed before 48 hours after the start of IMV, 96 for deep-seated MSSA infections not involving pneumonia, 42 patients with non-aureus staphylococcal infections, 9 MRSA VAP, 11 post-mortem diagnoses and 16 redundancies. 131 patients were finally included. More than half (51.1%) had monobacterial MSSA VAP. Regarding treatment, 21 patients (16%) received a cefazolin course and 47 (36%) were administered cloxacillin. The remaining 74 patients (56%) received another antimicrobial treatment.

Figure 1. Flow chart



VA: ventilator-associated; MSSA: methicillin-sensitive Staphylococcus aureus; MRSA: methicillin-resistant Staphylococcus aureus; VAP: ventilator-associated pneumonia; 1/3/4GC: first/third/fourth generation cephalosporin

** Pneumonia diagnosed on patients without invasive mechanical ventilation or prior to 48 hours after invasive mechanical ventilation onset*

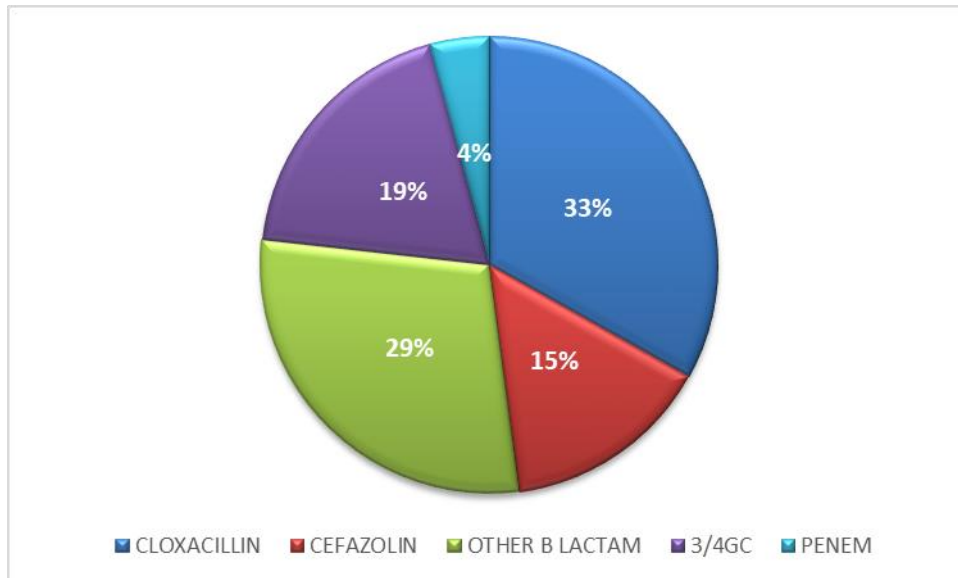
Demographic data, medical background of the overall cohort and MSSA VAP characteristics at diagnosis are presented in **Table 1**. Patients were mostly males (69%), with a median age of 54 years [43-66], and a median Charlson comorbidity score of 2.4 [0-4]. An underlying immunosuppression was rare (7%). Immunocompromised conditions included solid organ transplant (n=2), malignant neoplasia or hemopathy (n=4), recent chemotherapy (n=1), detectable HIV infection (n=1) and systemic inflammatory disease treated with immunosuppressive therapy (n=2). A third of the overall population (32%) was admitted for COVID-19 induced ARDS while 18% had cerebrovascular events (either ischemic or hemorrhagic), 13% a traumatic brain injury, 12% a cardiac arrest, 9% an ARDS from other cause than COVID-19 infection, and 1% a septic shock. The remaining 15% were admitted in ICU for myasthenia gravis, Guillan-Barre syndrome, lateral amyotrophic sclerosis, status epilepticus, non-neurological polytrauma, mesenteric ischemia, acute pancreatitis, diabetic

ketoacidosis, mitochondrial disease, acute renal failure on compartment syndrome, and intentional poisoning. Severity scores at admission highlighted a 15 to 27% predicted mortality in ICU (median SOFA = 6.87 [4-10] and median IGS II = 41 [31-51]), and an actual 27.5% mortality rate in the overall cohort was observed. Most of the patients were mechanically ventilated during the first 24 hours of their admission (77%) and presented a median PaO₂/FiO₂ ratio of 234 under volume controlled mode for 73% of them. During their ICU stay and prior to the MSSA VAP diagnosis, 44% of the patients presented at least one episode of bacterial VAP (with other documentation than MSSA) and only 37.4% patients were antibiotic-free. Indeed, 63% of patients received at least one antimicrobial course prior to MSSA VAP, including 62% targeting MSSA and 10% targeting MRSA. None of the patients carried pulmonary MDR bacteria prior to MSSA VAP and rectal MDR carriage was detected in 11% of the cohort (extended spectrum beta-lactamase – ESBL – enterobacteriaceae). Blood analyses at MSSA VAP diagnosis shown in **Supplemental data** revealed slight anemia (median hemoglobin of 106g/L), elevated inflammation parameters (median C reactive protein at 147mg/L [3.5-450] and median procalcitonin at 2.7µg/L [0.06-44]), normal coagulation markers (median prothrombin time of 83% [73-93]) and normal kidney function with median creatinine of 85µmol/L [53-94] and median creatinine clearance of 97mL/min [70-121].

Regarding MSSA VAP characteristics at diagnosis, two third of the cohort displayed an ARDS with a median PEEP of 10 cmH₂O [7-12] and a median PaO₂/FiO₂ ratio of 156 [122-193]. Only 5% of the patients required VV-ECMO. At MSSA VAP diagnosis most of patients had fever (97%) and worsening gas exchange (89%). MSSA was accountable for lone pneumonia in most patients (91%) as only few of them presented with concomitant bacteremia (8%) or several infected sites (5%). The infection was mainly acquired during the hospital stay (65%) and mostly detected by ETA (92%). Pulmonary co-infections were frequent, led by bacterial co-infections (50%), viral co-infections (36%), the latter mainly represented by COVID-19 infection, and only 3 cases of fungal co-infections were reported (pulmonary aspergillosis). There was a tendency to more viral co-infections in the cefazolin group compared to cloxacillin (51% versus 40% respectively, p = 0.432) but the cloxacillin group presented a slightly higher frequency of bacterial co-infections than cefazolin (34% versus 14% respectively, p = 0.144). 75% of patients received a probabilistic antimicrobial course prior to MSSA identification. All of the patients receiving a probabilistic course were administered a MSSA-targeting antimicrobial. Treatment was then adjusted to cloxacillin (n = 47, 33%), cefazolin (n = 21, 16%), other beta-lactam (n = 41, 31%) (*i.e.*: amoxicillin-clavulanate or piperacillin-

tazobactam), 3/4GC (n = 27, 21%) or penems (n = 6, 5%) in combination or not with aminoglycoside for a median duration of 7 days [6-9] as shown in **Figure 2**. Slightly more patients in the cefazolin group also received a combination with aminoglycoside than in the cloxacillin group, although not reaching statistical significance (90.5% versus 83%, p = 0.712).

Figure 2. Clusters of patients according to antimicrobial treatment targeting MSSA VAP.

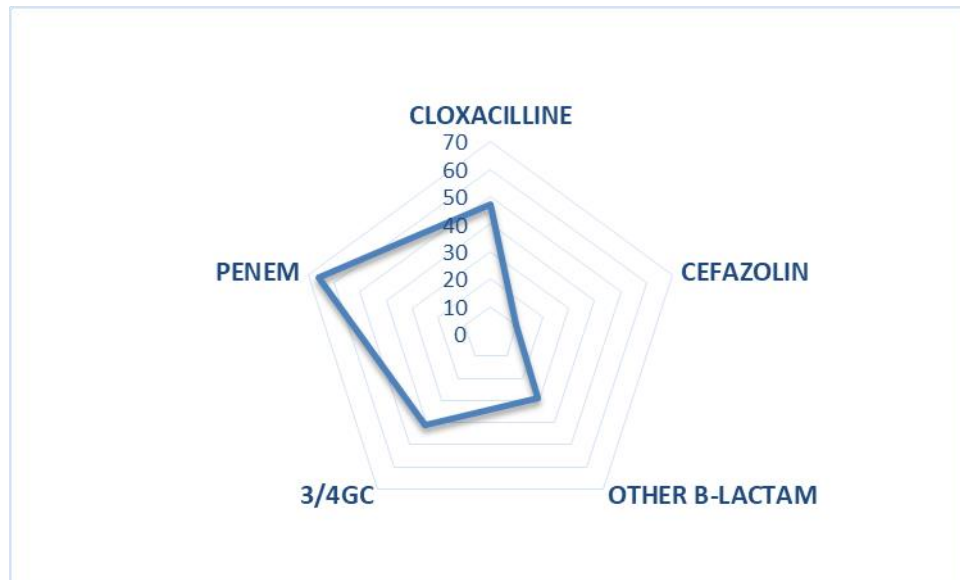


MSSA: methicillin-susceptible Staphylococcus aureus; VAP: ventilator-associated pneumonia; other B-lactam: amoxicillin-clavulanate or piperacillin-tazobactam; 3/4GC: third or fourth generation cephalosporin

A successful outcome was observed in 66% of patients. Only 57% of antibiotic plasmatic dosing were within target ranges (only 61/131 plasmatic dosage were available). In the cloxacillin group, only 13 plasmatic dosing were available, among which 3 were within the targeted ranges (23%). In the cefazolin group, 19/21 plasmatic dosing were available, among which 13 were within the targeted ranges (68%). Microbiological clearance was obtained for 53% of the cohort. Percentages of treatment failure are described in **Figure 3**. Among patients with treatment failure, 6 presented a MSSA colonization, 29 a persistent MSSA VAP (2 with cefazolin course and 11 with cloxacillin course) and 20 died, including 10 respiratory-linked deaths. An 8.42% rate of AEs was noted, including 1 *Clostridium difficile* colitis (under beta-lactam treatment), 9 acute kidney injuries (5 cloxacillin-induced acute kidney injury –AKI–, 1 beta-lactam-induced AKI, and 3 3/4GC-induced AKI) and only 1 patient displayed a grade 1 cefazolin-induced coagulopathy, the latter resolving prior to the end of the antimicrobial course. Cefazolin led to a lower incidence of AEs than cloxacillin although not reaching statistical

significance (4.8% versus 10.6% respectively, $p = 0.66$) and no serious AE was observed with cefazolin contrarily to cloxacillin (0% versus 4.2% respectively, $p = 0.99$).

Figure 3. Percentage of treatment failure according to the administered antibiotics targeting MSSA VAP.



MSSA: methicillin-susceptible Staphylococcus aureus; VAP: ventilator-associated pneumonia; 3/4GC: third or fourth generation cephalosporin

Factors associated with treatment failure

Patients were compared according to the outcome of MSSA VAP treatment (failure versus success) in univariate analysis as shown in **Table 2**. Patients with treatment failure were rather men ($p = 0.013$), older patients ($p = 0.029$), and patients with a higher Charlson index ($p = 0.018$). Bacteremia ($p = 0.008$), fungal co-infection ($p = 0.015$), and another choice of antibiotic than cefazolin ($p = 0.003$) were also associated with more treatment failure. Expectedly, a significantly greater mortality rate was reported in the treatment failure group (19% versus 44%, $p = 0.003$). Patients in the cefazolin group tended to have a lower incidence of recurrence/relapse of MSSA VAP compared to cloxacillin (9.5% versus 23% respectively, $p = 0.316$). ARDS, bacterial or viral co-infections, administration of a probabilistic antibiotic course, adverse events, plasmatic dosing within the therapeutic targets and occurrence of new MDR carriage were not associated with therapeutic failure. The duration of antibiotic course was similar in both groups ($p = 0.435$).

All five significant parameters of treatment failure in univariate analysis with a p threshold of 0.05 were retained for the multivariate analysis, respecting the ratio of 1 variable for 10 events. The age was discarded to avoid redundancies with the Charlson index. Independent factors associated with treatment failure are exposed in **Table 3**. Female gender (OR = 0.327, 95% CI 0.1 – 0.713, p = 0.008) and cefazolin treatment (OR = 0.3, 95% CI 0.042 – 0.895, p = 0.03) were protective factors. However, MSSA bacteremia was at risk of treatment failure (OR = 3.832, 95% CI 1.01 – 32.2 p = 0.048). Higher Charlson comorbidity index and whether or not receiving probabilistic antimicrobial therapy were not at risk of treatment failure (OR = 1.150, 95% CI 0.950 – 1.435, p = 0.146 and OR = 0.196, 95% CI 0.497 – 3.819, p = 0.596 respectively).

DISCUSSION

In a cohort of 131 patients diagnosed with MSSA VAP, treatment with cefazolin was associated with treatment success in multivariate analysis. Likewise, female gender was a protective factor. Higher Charlson comorbidity index and concomitant MSSA VAP bacteremia were associated with treatment failure. Overall VAP-attributable mortality in ICU ranges from 10 to 50% in literature.¹ Thus, adequate and targeted course of antimicrobial agent is essential. In our study, 44% of patients with treatment failure died compared to 19% in the group of treatment success, which reinforces the challenge of a favorable treatment outcome.

Recent literature regarding the outcome of MSSA infections according to the chosen antimicrobial agent revealed encouraging results as cefazolin was equally effective as ASP (any infection including the deep-seated ones).^{9,10,29–32} Further studies described a superiority of cefazolin over ASP for the treatment of MSSA infections with earlier discharge of hospitalized patients³³, less overall cost³³, lower all-cause mortality and lower rates of clinical failure.¹³ McDanel et al. described a 37% reduction in 30-day mortality and a 23% reduction in 90-day mortality for patients treated with cefazolin compared with ASP.¹⁵ Pharmacokinetics was also in favor of cefazolin use as therapeutic plasmatic targets were faster achieved than with ASPs.¹⁴ Indeed, slightly more patients achieved plasmatic dosing of antibiotics within targets with cefazolin compared to cloxacillin (68% versus 23%, p = 0.20). These results seem to be enhanced by higher daily doses of cefazolin in ICU patients (8g/day versus 6g/day)¹², as this specific population usually displays greater distribution volume and glomerular hyperfiltration.^{34,35} Although standard doses of cefazolin (6g/day) were used in our study, the

latter demonstrated cefazolin as associated with treatment success in the management of MSSA VAP (OR for treatment failure = 0.3 95%CI 0.042-0.86, $p = 0.030$). Apart from the meta-analysis published by Allen et al.¹³, the studies failed to reach statistical significance regarding recurrence/relapse of MSSA infections with cefazolin compared with ASP^{9,29,33}, describing higher²⁹ or lower tendencies.^{31,33} In our cohort, cefazolin tended to be associated with a lower incidence of recurrence/relapse of MSSA VAP than cloxacillin (9.5% versus 23% respectively, $p = 0.316$). To properly answer the debate, an ongoing randomized controlled trial (CloCeBa) has been proposed by Burdet et al. based on the hypothesis of a non-inferior efficacy of cefazolin in comparison to cloxacillin in the treatment of MSSA bacteremia.³⁶

In light of the reports in literature and our results, cefazolin appears to be effective and usable as a first-line agent for MSSA VAP. Besides, cefazolin has recently been reported to be safer than cloxacillin in the treatment of MSSA infection. Indeed, its use was associated with lower rates of adverse events than ASPs^{9,10,13,31,37} (*i.e.* the first-line antimicrobial recommended for this pathology⁶), resulting in fewer treatment discontinuations, even at higher dosages.³³ In our cohort, cefazolin was associated with a lower incidence of AEs than cloxacillin although not reaching statistical significance (4.8% versus 10.6% respectively, $p = 0.66$) probably due to the small number of events. No serious AE was reported with cefazolin whilst cloxacillin was associated with 2 grade 3 AKI (thus 0% versus 4.2%, $p = 0.99$). However, specifically in the context of traumatic brain injury or vitamin K deficiency, practitioners must closely monitor coagulation parameters to prevent the hemorrhagic risk and the development of cefazolin-induced coagulopathy.³⁸ It should be noted that in our cohort, the patients in the cefazolin group displayed a higher comorbidity index (1.45 versus 3 Charlson score, $p 0.04$) probably due to the younger age (one of the parameters of the Charlson score) of patients in this group compared to cloxacillin (49 versus 59 years-old respectively, $p 0.02$). However, the cefazolin group had a slightly higher SOFA and IGS II scores. (**Appendix.**)

In our study, MSSA bacteremia associated with MSSA VAP was correlated with a higher risk of treatment failure (OR = 3.83, 95% CI 1.011 – 32.2, $p = 0.048$). In this particular context, practitioners may need to extend the antibiotic duration beyond the recommended 7 days or prescribe a combination of antimicrobials to avoid treatment failure.³⁹ In our study, the duration of antibiotic therapy had no impact on the outcome, probably because the durations between the two groups (success versus failure) were similar (8.2 versus 7.6 days respectively, $p = 0.435$).

The strengths of our study encompass the “real-world” population of polyvalent ICUs. Besides, our cohort displayed a relatively low incidence of MDR bacteria carriage (0% in lungs and 11% MDR *Enterobacteriaceae* in rectal samples), thus preventing the overuse of broad spectrum antimicrobials and occurrence of a MDR nosocomial infection.⁴⁰⁻⁴³ Finally, to our knowledge, this is the first study focusing exclusively on MSSA VAP treatment and comparing the outcome according to the administered antimicrobial. The limits of our study first include its retrospective and monocentric design. Besides, the Microbiology department of our University Hospital did not provide quantitative results for distal bronchial samples but rather qualitative binary microbiological evidence.⁴⁴ Third, the patients administered with cefazolin received the standard dose of 6g/day rather than 8g/day, the latter being associated with greater clinical success, lower overall mortality rate and decreased rate of MSSA pneumonia recurrence.¹² Thus, the results we obtained might be enhanced in a further study with higher cefazolin daily dose. The plasmatic antibiotic dosage was lacking for more than half of the cohort, a bias attributable to the retrospective design of the study.

CONCLUSION

Cefazolin treatment for *Methicillin-susceptible Staphylococcus aureus* ventilator-associated pneumonia in the intensive care unit was independently associated with treatment success and displayed fewer adverse events than with cloxacillin. In light of recent literature and our study regarding efficacy and safety, cefazolin could replace ASP as the first-line agent for MSSA VAP in ICU although these results need to be confirmed by randomized controlled trials.

Table 1. Population characteristics

| | | Patients <i>n</i> = 131 |
|---|--|-----------------------------------|
| DEMOGRAPHIC DATA | | |
| Age (years) | | 54 [15-81] |
| Gender (male), <i>n</i> (%) | | 92(70) |
| Charlson comorbidity score | | 2.4 [0-4] |
| SOFA score at admission | | 6.87 [4-10] |
| IGS II score at admission | | 41 [32-51] |
| MOTIVE OF ADMISSION, <i>n</i>(%) | | |
| Brain trauma injury | | 17(13) |
| COVID-19-induced ARDS | | 42(32) |
| ARDS from other cause | | 12(9) |
| Cardiac arrest | | 16(12) |
| Sepsis / septic shock | | 1(1) |
| Cerebrovascular event | | 24(18) |
| Other | | 19(15) |
| PRIOR TO MSSA VAP | | |
| Stay in ICU (days) | | 7.3 [3-9] |
| Duration of IMV (days) | | 6.25 [2-8] |
| Pulmonary MDR carriage, <i>n</i> (%) | | 0 (0) |
| Rectal MDR carriage, <i>n</i> (%) | | 14(11) |
| Viral pneumonia, <i>n</i> (%) | | 48(37) |
| Bacterial pneumonia/VAP, <i>n</i> (%) | | 58(44) |
| Antibiotic course, <i>n</i> (%) | | 82(63) |
| AT MSSA VAP DIAGNOSIS | | |
| SOFA | | 10 [7-12] |
| ARDS, <i>n</i> (%) | | 87(66) |
| Worsening gas exchange, <i>n</i> (%) | | 117(89) |
| Fever, <i>n</i> (%) | | 100(97) |
| Lone pneumonia, <i>n</i> (%) | | 119(91) |
| Bacteremia, <i>n</i> (%) | | 11(8) |
| MSSA several infected sites, <i>n</i> (%) | | 6(5) |
| MICROBIOLOGY | | |
| VIRAL CO-INFECTION, <i>n</i> (%) | | 47 (36) |
| Herpesviridae, <i>n</i> (%) | | 5 (4) |
| BACTERIA CO-INFECTION, <i>n</i> (%) | | 66 (50) |
| Gram positive bacteria, <i>n</i> (%) | | 10 (8) |
| Gram negative bacteria, <i>n</i> (%) | | 57 (44) |
| FUNGAL CO-INFECTION, <i>n</i> (%) | | 4 (3) |
| VAP PROBABILISTIC COURSE, <i>n</i> (%) | | 98 (75) |
| NEW MDR CARRIAGE | | 24 (19) |
| OUTCOME | | |
| IMV duration | | 16 [9-27] |
| Microbiological clearance | | 60 (53) |
| Success | | 86 (66) |
| Death | | 36 (27.5) |

ICU: intensive care unit; MSSA: methicillin-susceptible Staphylococcus aureus; VAP: ventilator-associated pneumonia; ARDS: acute respiratory distress syndrome; SOFA: sepsis-related organ failure assessment; IGS: index de gravité simplifié; ; IMV : invasive mechanical ventilation; ; MDR : multidrug

resistant bacteria . Variables are presented in medians with interquartile range of 25% and 75% [IQR25-75].

Table 2. Risk factors of therapeutic failure in 131 MSSA VAP patients admitted in ICU in univariate analysis.

| PATIENTS | SUCCESS n=86 | FAILURE n=45 | p value* |
|--|---------------|---------------|---------------|
| DEMOGRAPHIC DATA | - | - | - |
| Age | 55 [39-65] | 61 [48-72] | 0.029 |
| Female, n(%) | 82 (95) | 18 (40) | 0.013 |
| Charlson comorbidity score | 2.07 [0-4] | 3.0 [0-5] | 0.018 |
| AT MSSA VAP DIAGNOSIS | - | - | - |
| SOFA | 9 [6-12] | 10 [7.5-12.5] | 0.091 |
| RESPIRATORY STATUS | - | - | - |
| ARDS | 53 (62) | 34 (76) | 0.123 |
| PEEP | 8 [6-12] | 10 [8-12] | 0.339 |
| VV-ECMO | 4 (67) | 2 (33) | 0.957 |
| PaO ₂ /FiO ₂ ratio | 160 [130-200] | 144 [113-180] | 0.06 |
| Worsening gas exchange | 74 (86) | 43 (96) | 0.028 |
| SEPTIC CONDITION | - | - | - |
| Fever | 61 (77) | 30 (71) | 0.483 |
| Lone pneumonia | 81 (94) | 38 (84) | 0.107 |
| Bacteremia | 3 (4) | 8 (18) | 0.008 |
| Several infected sites | 4 (5) | 2 (4) | 0.957 |
| Community-acquired MSSA | 32 (37) | 14 (31) | 0.487 |
| MICROBIOLOGY | - | - | - |
| Viral co-infection | 28 (33) | 19 (43) | 0.335 |
| Bacterial co-infection | 41 (48) | 25 (56) | 0.392 |
| Fungal co-infection | 0 (0) | 3 (7) | 0.015 |
| ANTIBIOTIC TREATMENT | - | - | - |
| PROBABILISTIC COURSE | 63 (73) | 35 (78) | 0.571 |
| MSSA TARGETING COURSE | - | - | - |
| Cloxacillin (+/- aminoglycoside) | 25 (29) | 22 (49) | 0.073 |
| Cefazolin (+/- aminoglycoside) | 19 (22) | 2 (4) | 0.003 |
| Other B-lactam (+/- aminoglycoside) | 29 (34) | 12 (27) | 0.408 |
| 3/4GC (+/- aminoglycoside) | 16 (19) | 11 (24) | 0.827 |
| Penem (+/- aminoglycoside) | 2 (2) | 4 (9) | 0.180 |
| Antibiotic duration (days) | 7 [6-9] | 7 [6-10] | 0.435 |
| Plasmatic dosing within targets | 29 (63) | 6 (40) | 0.142 |
| Adverse events | 3 (3.5) | 0 (0) | 0.551 |
| New MDR carriage | 14 (17.5) | 10 (22) | 0.520 |
| OUTCOME | - | - | - |
| Clinical improvement | 78 (91) | 6 (13) | 0.000 |
| IMV duration (days) | 18 | 35 | 0.014 |
| Microbiological clearance | 50 (71) | 10 (23) | 0.0001 |
| Death | 16 (19) | 20 (44) | 0.003 |

MSSA: methicillin-susceptible *Staphylococcus aureus*; VAP: ventilator-associated pneumonia; ICU: intensive care unit; ARDS: acute respiratory distress syndrome; SOFA: sepsis-related organ failure assessment; IGS: index de gravité simplifié; PEEP: positive end-expiratory pressure; NIV: non-invasive ventilation; IMV: invasive mechanical ventilation; VV ECMO: venovenous extracorporeal membrane oxygenation; PT: prothrombin time; LDH: lactate dehydrogenase; CRP: C reactive protein; AKI : acute kidney injury; MDR: multidrug resistant

* p was considered significant if < 0.05

Table 3. Adjusted odds ratios in multivariate analysis for risk factors of therapeutic failure in 131 MSSA VAP patients admitted in ICU.

| FACTORS* | OR | 95% CI | p |
|----------------------------|------|-----------|--------------|
| Sex (female) | 0.32 | 0.1-0.71 | 0.008 |
| Charlson comorbidity index | 1.15 | 0.95-1.43 | 0.146 |
| Probabilistic antibiotic | 1.19 | 0.49-3.81 | 0.596 |
| Bacteremia | 3.83 | 1.01-32.2 | 0.048 |
| Cefazolin | 0.3 | 0.04-0.89 | 0.030 |

MSSA: methicillin-susceptible *Staphylococcus aureus*; VAP: ventilator-associated pneumonia; ICU: intensive care unit; OR: odds ratio; CI: confidence interval

* All five significant parameters of treatment failure in univariate analysis with a p threshold of 0.05 were retained for the multivariate analysis, respecting the ratio of 1 variable for 10 events. The age was discarded to avoid redundancies with the Charlson index.

Supplemental data. Lab results at MSSA VAP diagnosis and MSSA detection method.

| | | Patients n = 131 |
|----------------------------------|--|---------------------|
| LAB RESULTS | | |
| Hemoglobin (g/L) | | 106.4 [92-120] |
| Platelets (G/L) | | 283.3 [171-332] |
| Fibrinogen (g/L) | | 6.8 [5.4-8.3] |
| Leukocytes (G/L) | | 12.85 [9.3-15] |
| Neutrophils (G/L) | | 10. [7.2-12.1] |
| Lymphocytes (G/L) | | 1.13 [0.67-1.6] |
| PT (%) | | 83 [73-93] |
| LDH (U/L) | | 432 [284-530] |
| Creatinin (μmol/L) | | 85.6 [53-94] |
| Renal clearance CKD EPI (mL/min) | | 97.6 [70-121] |
| CRP (mg/L) | | 147 [55.3-227.3] |
| Procalcitonin (μg/L) | | 2.7 [0.2-1.5] |
| MSSA DETECTION | | - |
| BAL, n(%) | | 44 (34) |
| PSB, n(%) | | 27 (21) |
| ETA, n(%) | | 120 (92) |
| At least two method, n(%) | | 56 (44) |

MSSA: methicillin-susceptible *Staphylococcus aureus*; VAP: ventilator-associated pneumonia; PT: prothrombin time; LDH: lactate dehydrogenase; CRP: C reactive protein ; BAL : bronchoalveolar lavage ; PSB : protected specimen brush ; ETA : endotracheal aspirate

Variables are presented in medians with interquartile range of 25% and 75% [IQR25-75].

Appendix. Comparison of cefazolin and cloxacillin for MSSA VAP treatment in ICU patients.

| PATIENTS | Cefazolin n=21 | Cloxacillin n=47 | P* |
|----------------------------------|-------------------|---------------------|-------------|
| DEMOGRAPHIC DATA | | | - |
| Age (years) | 49 [31-59] | 59 [51-70] | 0.02 |
| Gender (male) | 11 (55%) | 35 (74%) | 0.09 |
| Charlson comorbidity score | 1.45 [0-2] | 3 [1-4] | 0.04 |
| Immunosuppression | 1 (4.8%) | 5 (11%) | 0.65 |
| MOTIVE OF ADMISSION, n(%) | | | |
| Brain trauma injury | 2 (9.5) | 5 (10.6) | 0.90 |
| COVID-19-induced ARDS | 10 (47.7) | 19 (40.4) | 0.73 |
| ARDS from other cause | 0 (0) | 7 (14.8) | 0.28 |
| Cardiac arrest | 2 (9.5) | 5 (10.6) | 0.90 |
| Sepsis / septic shock | 0 (0) | 0 (0) | - |
| Cerebrovascular event | 3 (14.3) | 6 (12.7) | 0.88 |
| Other | 4 (19) | 5 (10.6) | 0.67 |
| AT MSSA VAP DIAGNOSIS | | | |
| SOFA | 9.19 [7-11] | 9.1 [6,5-12] | 0.93 |
| IGS II | 39.6 [30-52] | 38.4 [32-45] | 0.60 |
| ARDS | 14 (70%) | 32 (68%) | 0.98 |
| Worsening gas exchange | 17 (85%) | 35 (95%) | 0.85 |
| Bacteremia | 0 (0%) | 6 (13%) | 0.17 |
| MICROBIOLOGY | | | |
| VIRAL CO-INFECTION | 11 (51%) | 19 (40%) | 0.432 |
| BACTERIAL CO-INFECTION | 3 (14%) | 16 (34%) | 0.144 |
| ANTIBIOTIC TREATMENT | | | |
| Aminoside | 19 (90.5%) | 39 (83%) | 0.712 |
| Antibiotic duration (days) | 7.6 [4-7] | 8.1 [4-10] | 0.14 |
| SAFETY | | | |
| Plasmatic dosing within targets | 13/19 (68%) | 3/13 (23%) | 0.2 |
| AEs | 1 (4.8%) | 5 (10.6%) | 0.66 |
| Severe AEs | 0 (0%) | 2 (4.2%) | 0.99 |
| OUTCOME | | | |
| Successful | 19 (95%) | 25 (53%) | 0.03 |
| Renal clearance | 11/19 (58%) | 24 (51%) | 0.79 |
| Persistent colonisation | 6 (31%) | 7 (15%) | 0.2 |
| Relapse / recurrence MSSA VAP | 2 (9.5%) | 11 (23%) | 0.316 |
| Death | 3 (14.3%) | 14 (29.8%) | 0.23 |

MSSA: methicillin-susceptible Staphylococcus aureus; VAP: ventilator-associated pneumonia; ICU: intensive care unit; SOFA: sepsis-related organ failure assessment; IGS: index de gravité simplifié; ARDS: acute respiratory distress syndrome ; Aes : adverse events ; severe Aes : ≥ grade 3 Aes

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III/ CONCLUSION

En conclusion, cette étude visait à identifier les facteurs de risque indépendants associés à l'échec du traitement chez les patients atteints de pneumonie acquise sous ventilation mécanique due à *Staphylococcus aureus* sensible à la méthicilline en soins intensifs. Notre travail retrouve des facteurs de risques d'échec thérapeutique déjà décrits dans la littérature. Les facteurs de risques concernent principalement le terrain et comorbidités des patients atteints. Nous montrons aussi que les PAVM bactériémiantes ont elles-aussi plus de risque d'échecs thérapeutiques.

Ensuite notre travail confirme notre hypothèse principale qui était que la cefazoline était supérieure à la cloxacilline. On retrouve effectivement dans l'analyse multivariée principale, ainsi que dans les différentes analyses univariées en sous groupe, que la céfazoline était un facteur protecteur indépendant d'échec thérapeutique. Résultat qui reste à être confirmé au travers d'une étude randomisée contrôlée.

Enfin, un des derniers objectifs de cette étude était de décrire et comparer les effets indésirables des traitements antibiotiques. On retrouve une différence non significative avec davantage d'effet indésirable en utilisant la cloxacilline que la céfazoline. Cette tendance reste elle aussi à être démontrée dans une étude randomisée contrôlée.

SERMENT D'HIPPOCRATE

Au moment d'être admis à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité.

Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux.

Je respecterai toutes les personnes, leur autonomie et leur volonté, sans **aucune discrimination selon leur état ou leurs convictions**. J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité. Même sous la contrainte, je ne ferai pas **usage de mes connaissances contre les lois de l'humanité**.

J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences.

Je ne tromperai **jamais leur confiance** et **n'exploiterai pas le pouvoir hérité** des circonstances pour forcer les consciences.

Je donnerai mes soins à l'indigent et à quiconque me les demandera. Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.

Admis dans l'intimité des personnes, je tairai les secrets qui me seront confiés. Reçu à l'intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les mœurs.

Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission. Je n'entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.

J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité.

Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses ; que je sois déshonoré et méprisé si j'y manque.

Evaluation des facteurs de risques d'échecs thérapeutiques dans le traitement des pneumopathies acquises sous ventilation mécanique à *Staphylococcus Aureus* sensible à la méticilline.

Résumé

Contexte : Les pneumonies acquises sous ventilation mécanique (PAVM) sont fréquentes et associées à une morbi-mortalité importante chez les patients de réanimation sous ventilation mécanique invasive pendant plus de 48 heures. Parmi les PAVM documentées, le *Staphylococcus aureus* méticilline-sensible (SAMS) est responsable de 10 à 25% des PAVM. Les pénicillines antistaphylococciques (PAS) constituent le traitement de première intention de ces PAVM à SAMS malgré leur indisponibilité fréquente due à des ruptures de stock, leurs multiples effets indésirables (EIs) et leur efficacité récemment controversée en comparaison avec la céfazoline (céphalosporine de première génération).

Méthode : Afin de déterminer les facteurs de risque d'échec thérapeutique des PAVM à SAMS, nous avons mené une étude rétrospective monocentrique dans une réanimation polyvalente française sur une période de 6 ans.

Résultats : Parmi une cohorte de 131 patients, les facteurs tels que l'âge plus avancé (p 0.029), un score de fragilité plus élevé (index de Charlson, p 0.018), et la présence d'une co-infection fongique (aspergillose pulmonaire invasive p 0.015) étaient associés à l'échec thérapeutique des PAVM à SAMS. De même, une bactériémie concomitante de la PAVM était indépendamment associée à l'échec thérapeutique (OR 3.83, 95% CI 1.011 – 32.2, p 0.048). A contrario, le sexe féminin (OR: 0.327, 95% CI 0.1 – 0.713, p 0.008) et le traitement par céfazoline (OR 0.3 95%CI 0.042-0.86 p 0.030) constituaient des facteurs protecteurs contre l'échec thérapeutique. De plus, la céfazoline était associée à une tendance à la diminution des EIs (4.8% versus 10.6%, p 0.66) par rapport à la cloxacilline (PAS) ainsi qu'à moins de rechute/récidive de PAVM à SAMS (9.5% versus 23%, p 0.316).

Conclusion : Dans cette étude et de manière congruente avec la littérature, l'âge, le sexe masculin, et les bactériémies étaient indépendamment associés au risque d'échec thérapeutique des PAVM à SAMS. Le traitement par céfazoline était indépendamment associé au succès thérapeutique et était mieux toléré que la cloxacilline.

Mots-clés : Pneumopathie acquise sous ventilation mécanique, PAVM, *Staphylocoque aureus* sensible à la méticilline, SAMS, soins intensifs, cefazoline, échec thérapeutique.