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# **Pneumopathie acquise sous ventilation mécanique chez des patients atteints de SARS-CoV-2 en réanimation: une étude de cohorte rétrospective de Mars à Novembre 2020**

Jacques Moreno

► **To cite this version:**

Jacques Moreno. Pneumopathie acquise sous ventilation mécanique chez des patients atteints de SARS-CoV-2 en réanimation: une étude de cohorte rétrospective de Mars à Novembre 2020. Sciences du Vivant [q-bio]. 2022. dumas-03839775

**HAL Id: dumas-03839775**

**<https://dumas.ccsd.cnrs.fr/dumas-03839775v1>**

Submitted on 4 Nov 2022

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**Pneumopathie acquise sous ventilation mécanique chez des patients  
atteints de SARS-CoV-2 en réanimation: une étude de cohorte  
rétrospective de Mars à Novembre 2020**

**T H E S E     A R T I C L E**

**Présentée et publiquement soutenue devant  
LA FACULTÉ DES SCIENCES MEDICALES ET  
PARAMEDICALES  
DE MARSEILLE**

**Le 28 Octobre 2022**

**Par Monsieur Jacques MORENO**

**Né le 29 mai 1993 à New York (Etats-Unis)**

**Pour obtenir le grade de Docteur en Médecine**

**D.E.S. d' ANESTHESIE REANIMATION**

**Membres du Jury de la Thèse :**

**Monsieur le Professeur GAINNIER Marc**

**Président**

**Monsieur le Docteur (MCU-PH) DUBOURG Grégory**

**Assesseur**

**Monsieur le Docteur CARVELLI Julien**

**Directeur**

**Monsieur le Docteur BREULEUX Christophe**

**Assesseur**



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RUFO Marcel  
SAHEL José  
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VAGUE/JUHAN Irène

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Mme le Professeur	JUHAN-VAGUE Irène	31/08/2011
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M. le Professeur	ROBERTOUX Pierre	31/08/2011

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M. le Professeur	VERVLOET Daniel	31/08/2012

### 2010

M. le Professeur	MAGNAN Jacques	31/12/2014
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M. le Professeur	OLIVER Charles	31/08/2018
M. le Professeur	SEBBAHOUN Gérard	31/08/2018

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<b>1986</b> MM. les Professeurs	E. MIHICH (U.S.A.) T. MUNSAT (U.S.A.) LIANA BOLIS (Suisse) L.P. ROWLAND (U.S.A.)

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BARGIER Jacques (MCF associé Méd. Gén. À mi-temps)  
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REYNAUD Rachel (PU-PH)  
TSIMARATOS Michel (PU-PH)

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## REMERCIEMENTS

Tout d'abord, je souhaite remercier mes membres du jury.

Merci au président du jury, le Professeur Marc Gainnier pour avoir accepté de présider cette thèse, de m'avoir conseillé lors de son élaboration et d'avoir fait preuve d'une accessibilité et humanité particulière lors de mon semestre au sein de son équipe.

Merci à mon directeur de thèse, le Docteur Julien Carvelli, qui a grandement contribué à mon apprentissage pour devenir réanimateur et qui m'a également apporté de très bons conseils pour la réalisation de ce travail

Merci au Docteur Christophe Breuleux pour avoir accepté de participer à ce jury et d'avoir été un mentor et pédagogue précieux ces dernières années.

Merci au Docteur Grégory Dubourg pour avoir accepté d'évaluer ce travail, d'avoir participé à l'élaboration des données microbiologiques et de m'avoir aidé pour leurs interprétation.

Merci au Docteur Jérémy Bourenne pour m'avoir encadré, soutenu tout au long de ce projet. Ta disponibilité et bienveillance m'auront été indispensable pour mener ce projet à bout.

Merci à Mohamed Boucekine pour l'élaboration des données statistiques. Ta disponibilité et réactivité pendant ce travail auront été d'une grande aide.

Je remercie tous les médecins que j'ai eu la chance de rencontrer pendant mon externat à Grenoble et particulièrement le néphrologue Docteur Franco qui m'a montré que la sagesse, l'humilité et la douceur peuvent coexister en tant que soignant.

Je suis également très reconnaissant envers tous les médecins et services que j'ai pu fréquenter lors de mes années d'internat à Marseille et ses alentours.

Merci à l'équipe d'Avignon qui m'a enseigné que la recherche de l'excellence professionnelle, l'humour et la légèreté au travail ne sont pas contradictoires. Merci au Docteur Montini qui a été d'une écoute précieuse et de bons conseils en période de doute.

Merci à l'équipe du SAR Conception - RPPF qui m'a initié aux premières phases de l'autonomie, étape cruciale qui m'a permis de grandir et de prendre confiance en tant que médecin.

Merci à l'équipe d'anesthésie du bloc Nord qui m'a initié à la pratique de l'anesthésie et du bloc central de la Timone qui a renforcé mon désir pour celle-ci.

Un grand merci aux personnes travaillant à la Réanimation des Urgences de la Timone qui de par leur ferveur, résilience et optimisme sans faille m'ont apporté le désir et le courage nécessaire à poursuivre mon chemin.

Merci au Docteur Couadau de m'avoir accepté au sein de son équipe de réanimation au CHT de Nouméa. Expérience unique qui m'aura forgé à la médecine tropicale et introduit aux subtilités de la relation médecin patient de la culture mélanésienne.

Je remercie l'équipe d'anesthésie-réanimation pédiatrique m'a permis de découvrir une nouvelle facette de ma spécialité, autant fascinante professionnellement qu'enrichissante personnellement.

Merci à ma famille qui a toujours été présente et prête à me soutenir.

Merci à ma sœur qui a toujours su me faire rigoler et qui a été ma première patiente, tu te souviens ? Te quiero hermanita.

Merci à ma mère, qui m'a transmise les valeurs humaines d'Hippocrate sans aucune prétention de m'imaginer un jour devenir médecin.

Merci à mon père, d'avoir toujours priorisé ses enfants et d'être un modèle d'altruisme, que je m'efforce de suivre.

Merci à mon beau-père Thierry, d'avoir enrichi ma vie avec ta curiosité et ta bienveillance inégalable.

Merci à Tatiana, ma compagne, d'être venue embellir ma vie à plus d'un égard, par ton regard, ta vitalité, ton envie inexorable de profiter de chaque instant. Je ne serai pas le même médecin sans t'avoir rencontré.

Merci à ma belle-famille pour leur soutien et tous ces beaux moments passés ensemble.

Merci à ma mamie Lu, l'une des personnes les plus généreuses que je connaisse. T'avoir à ma soutenance me rend extrêmement fière et je sais que Papi l'aurait été aussi.

Merci à ma mamie Françoise de m'avoir transmis sa tendresse. Merci à mon grand-père paternel d'aimer me rappeler que je suis médecin comme son père.

Merci à tous mes cousins et pensée particulière à Sam, pour nos moments de discussion et de détente qui arrivent toujours à me ressourcer.

Merci à Dominique, Antoine et François, mes oncles et tantes d'avoir fait le déplacement pour ce moment spécial, qui l'est d'autant plus de par leur présence.

Merci à tous les autres membres de ma famille pour ces étés passés ensemble, source d'innombrables souvenirs.

Merci à mes amis de l'externat.

Merci à la Belette. Cette conversion doit honnêtement précéder les débuts de Facebook ! On a tout vécu, tout traversé ensemble. L'internat nous a un peu dispersé mais il est temps de remédier à cela !

Merci à Nico pour ton smile indélébile, qui ne t'a plus quitté depuis ce premier trimestre en radiologie, on commençait déjà les conneries ;)

Merci à Ben pour ta longévité. Premier pote de médecine c'est honorable ! Barcelone, Amsterdam, Thaïlande, Tignes, on a déjà bien bougé. Prochaine étape, les îles en post-internat ?!

Merci à Popo, d'être le moteur, le liant de notre groupe. Ta générosité en tant qu'amie et hôte nous ont permis de partager des moments inoubliables jusqu'au bout de la nuit !

Merci à Arthur d'être un vrai pote et d'avoir redoublé ta D3 avec moi ;) Nos aprem skis aux 7 Laux en sortie de stage me manque !

Merci à Théo de m'avoir toujours fait paraître minuscule à côté de ton corps de dieu grecque, on devrait prêter serment à Michaëlos pardi !

Merci à Vavou, tu as su trouver une façon de t'épanouir dans les deux mondes professionnels et personnels et j'espère qu'on repartagera des moments ensemble dans tes montagnes.

Merci à la team Koh-lantympiade pour tous ces week-ends, à déconner, picoler, suer, et découvrir des petits bouts du pays ensemble.

Merci à mes co-internes Marseillais qui m'ont toléré pendant ces quatre longues années.

Merci à Clem et Soso, la team inébranlable de Nord. C'était une autre époque j'avais les cheveux longs, mais j'étais déjà professeur ;)

Merci à la clique d'Avignon. Dam, Gab, Rems, on a parcouru du chemin depuis ce semestre ! Mais figurez-vous que j'ai toujours la même brosse à dent qui me retarde de quelques minutes. Et merci à Juju et Victorine d'avoir apporté un peu de douceur féminine pendant ce semestre.

Merci aux co-internes de la RDU qu'ils soient internistes, urgentistes, cardiologues ou anesthésistes-réanimateurs. Super semestre passé avec vous !



Merci la team de la RPPF, Pablo, Robin, Théo et Marie. Tellement content de ne plus jamais avoir à brancarder ces kilomètres jusqu'au scanner ! On s'est bien marré, soutenu et mine de rien, on a assez bien mangé aussi.

Merci à la bande d'anesth-réa pédiatrique ! On se sera malheureusement trop peu vu en dehors des murs de l'hôpital. Mais j'ai l'impression qu'on va se recroiser avec un certain nombre d'entre vous ;)

Merci à Axel, le vagabond n°1 de la promo, de m'avoir initié au Pico ! On se donne rendez-vous dans quel Dom-Tom alors ?

Merci à Philippe, pour ton soutien ces derniers mois, tu m'as donné l'énergie pour aller jusqu'au bout de ces interminables gardes de pédiatrie !

Merci à Pablo pour ton énergie débordante, ces sorties de grimpe auront mine de rien étaient trop rares ! On remet ça cet hiver ?

Merci à Antoine d'avoir chapoté le groupe ce semestre et de nous avoir régaler chez toi. Un kif monumental t'attend sur ton prochain semestre, profite-en !

Merci à Clem, ma co-interne la plus fidèle, de m'avoir fait marrer à plus d'une reprise et souvent diverti pendant ces longues journées de bloc ! On s'est trop peu vu en dehors, un de mes regrets. Je te souhaite que du bonheur pour la suite avec ta belle famille ;)

Merci à Soso, la plus marseillaise des belges que je connaisse ! Ton entrain et constante bonne humeur m'ont fait tellement plaisir ces dernières années ! Maintenant qu'on sait tous les deux plonger (et pas que dans l'alcool), à quand la sortie sur Marseille ?

Merci à Paulo et Cyril pour m'avoir appris qu'en post Sham l'anesthésie peut se pratiquer dans tous les états.

Merci à Geoffroy pour ton aide et ta patience envers mon incompetence quasi complète en stats !

Merci à Théo, le seul médecin (et ouais faut s'y remettre à la thèse gros !) communiste que je connaisse ! Ton rire communicateur a allégé cette année passée ensemble. J'espère que le carrefour de Fontaine t'as bien ressourcé, on s'y croisera peut-être dans le futur proche ;)

Merci à Denis, ce semestre d'anesth n'aurait pas été le même sans toi ! On va se prendre cette bière devant Axium j'ai l'impression aha.

Merci à Audrey, de m'avoir formé, écouté et conseillé en tant que co-interne puis chef et surtout d'avoir été à l'origine de l'improbable surnom *Pr Moreno*.

Merci à Audrey et Alexis, d'être devenus de véritables amis pendant ces années.

Merci à la team de la Nouvelle-Calédonie d'avoir participé à tant d'émotions et de bonheur, jamais un semestre n'aura été aussi intense !

Mention particulière pour THE couple du cailloux, Nico et Océ. Merci d'avoir été là, au bout du couloir et pourtant au bout du monde avec nous. La Fafa, c'est un truc qui ne s'efface pas.

Merci mes amis d'enfance, de la primaire aux dernières années de lycée, qui ont participé autant que ma famille à construire la personne que je suis aujourd'hui.

Thank you Elsa, for being by far the best friend any guy could ask for. When we were stuffing our faces with oreos and PB&Js who could've imagined we would end up where we are know. Even though we don't see each other as much, doesn't change the fact that it feels like only yesterday everytime we reunite. Who knows in the future we might live not that far again, Claix revisited here we come?? Haha

Love you dudette. Special shout out to Tom who I have a deep affection for.

Thank you Paul, my bro, my brother if ever I had one. Feels weird to say that it's been over ten years that our lives have been lived in different cities. Still, doesn't feel like that has affected our friendship, our 24 year friendship ! So happy how things have turned out for you and excited to get to know Hannah more! Can't wait for our next three-way bromance weekend with the Irishman. I love you man.

Speaking of, how can I not mention you ma man Max when thanking everyone involved in my medical journey. We started together, our paths separated but we've always been there for one another and I don't see that changing any time soon. Keep up the good work you're doing with that adorable Gabriel of yours ;) I love you bro.

Thank you to the Bonnieux team Claire, Amandine, Madeleine and Ewa! I have honestly known you guys for also many years but had to use that team name because that week was honestly one of the best ever! Just super laid back and chill, loved it! Waiting for the second episode to come out!

Thank you Raffaella, for having been there for so many years, and sharing those first years of medicine together made them easier to overcome. You love living life at its fullest more than anyone I know which is one of your greatest qualities. Just for all of your friends sake, take a chill pill every now and then, so this friendship can continue !

Jaicy, no idea if you will ever read this but thank you for being you, our American symbol that dreams do come true if you work hard and fight for what you want. That's actually a hard thing to do and the passion for what you do is truly inspiring. Haven't seen you in way too long, which is messed up.

Thank you Sandrine, a long-time friend and fellow member of the health community! You being here for this moment is really heartwarming. You deserve all the good things coming up soon in your life and I can only wish you all the best for the future ;)

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## I. RÉSUMÉ EN FRANÇAIS

### **Objectif**

Description des caractéristiques des pneumopathies acquises sous ventilation mécanique et mise en évidence des facteurs de risques associés, chez des patients atteints du COVID-19 hospitalisés en réanimation durant la première année de la pandémie de SARS-CoV-2.

### **Matériels et méthodes**

De Mars à Novembre 2020, inclusion de 161 patients infectés au SARS-CoV-2 ayant nécessité une ventilation mécanique, hospitalisés au sein de 7 services de réanimations de l'AP-HM.

Description des caractéristiques cliniques et microbiologiques des patients atteints de PAVM à travers la réalisation d'une étude rétrospective mono-centrique.

Comparaison des caractéristiques des patients atteints de PAVM avec les patients non atteints de PAVM afin de mettre en évidence des facteurs de risques éventuels.

Analyse uni-variée et multivariée des résultats.

### **Résultats**

82 sur 161 patients (51%) ont présenté au moins une PAVM durant leur hospitalisation en réanimation. Plus de trois quart étaient des hommes (77%) et 55% présentaient une hypertension artérielle chronique. 31/82 patients (38%) ont été traité par dexaméthasone et 47% ont reçu une antibiothérapie avant l'admission en soins intensifs.

88% des PAVM étaient tardives avec un délai médian d'apparition de 10 jours depuis la date d'intubation. Les bactéries à gram négatives représentaient 62% des souches documentées et *Pseudomonas spp* était l'espèce la plus représentée. 26/82 PAVM (32%) étaient liées à des bactéries multi-résistantes (BMR) avec comme principale mécanisme de résistance une céphalosporinase hyper-produite.

Les patients du groupe PAVM avaient des durées de ventilation mécanique, de séjour en réanimation et d'hospitalisation significativement plus longues que les patients sans PAVM.

Les analyses multivariées ont révélé que la dexaméthasone, l'âge, le sexe et le score ROX étaient des facteurs de risques de PAVM tandis que l'antibiothérapie débutée avant l'admission en réanimation était un facteur protecteur.

## **Conclusion**

La pneumopathie acquise sous ventilation mécanique est une complication de réanimation particulièrement fréquente au sein des patients COVID-19 ventilés atteignant un patient sur deux dans notre étude. Elle est responsable d'une hausse de morbidité du fait de l'augmentation de la durée d'hospitalisation et de séjour en soins intensifs. L'âge élevé, le sexe masculin et l'utilisation de la dexaméthasone sont des facteurs favorisant les PAVM. D'autres études de grandes ampleurs, s'intéressant à la dexaméthasone en particulier, sont nécessaires avant de remettre en cause ce traitement ayant fait preuve d'une baisse de mortalité dans le Sars-Cov-2.

## II. TRAVAIL DE THÈSE – VERSION ANGLAISE

### RESUME

#### Objective

Describe characteristics of ventilation-acquired pneumonia as well as potential risk factors associated in critically ill Sars-Cov-2 patients admitted in intensive care units during the first year of the COVID-19 pandemic.

#### Methods

From March to November 2020, inclusion of 161 patients infected with SARS-CoV-2 requiring mechanical ventilation and hospitalized in seven public hospital intensive care units in Marseille.

Description of clinical and microbiological characteristics of VAP by conducting a monocentric retrospective study. Comparison of VAP patient characteristics with patients haven't not developed VAP in order to identify possible risk factors.

Univariate and multivariate analysis of the results.

#### Results

82 patients out of 161 (51%) developed ventilation-acquired pneumonia. More than three quarters of them were men (77%) and 55% had hypertension.

31 out of 82 patients (38%) were treated with Dexamethasone and 47% received antibiotic treatments before ICU admission.

88% of respiratory infections were late VAP with a median delay of 10 days from the start of mechanical ventilation.

Gram negative bacteria were responsible for 62% of VAP with *Pseudomonas spp* being the most documented bacteria. Under a third (32%) of the ICU-acquired infections were from MDR bacteria and cephalosporin hyper production was the main antibiotic resistant mechanism.

Patients in the VAP group had significantly longer durations of mechanical ventilation and longer ICU and hospitalization lengths of stay compared to patients without VAP.

Multivariate analysis revealed that Dexamethasone, sex, age and the ROX score were risk factors for VAP whereas pre-ICU antibiotic treatment was a protective factor.

## **Conclusion**

Ventilation-acquired pneumonia is a particularly frequent ICU-related complication in ventilated COVID-19 patients, affecting one in two patients in our study. It is responsible for added morbidity through increased ICU and hospital length of stay. Old age, male gender and use of dexamethasone are factors favoring VAP. Further large-scale studies, focusing on dexamethasone in particular, are needed before questioning this treatment, which has proven to reduce mortality in Sars-Cov-2 patients.



## INTRODUCTION

The COVID-19 pandemic has, since late December 2019, created a global health crisis, infected millions of people and caused a significant number of deaths<sup>1</sup>. Thanks to broad anti-viral management care including wide-spread vaccination policies, Sars-Cov-2 related hospitalizations have decreased but its mutation prone genome coupled with concerns about duration of vaccine effectiveness explain why it is still a public health concern to this day<sup>2-5</sup>. In 2020, France faced two waves of infection, the first in spring and the second in autumn with a large number of patients admitted to the hospital and the intensive care units (ICU). This patient overflow saturated public hospital wards and critical care units, which in turn forced a rapid structural and labor force reorganization in order to maintain adequate health services. Sars-Cov-2 related symptoms vary from mild with fever, coughing, headaches and myalgia to severe with life threatening hypoxic respiratory failure<sup>6</sup>. In critically-ill adult patients, severe acute respiratory syndrome (SARS) is the main cause of organ failure and the need for mechanical ventilation is often required<sup>7,8</sup>. One of, if not the main complication of prolonged intubation is ventilator-acquired pneumonia (VAP). By increasing mechanical ventilation duration and hospital length of stay<sup>9,10</sup>, VAP is responsible for significant morbidity and an estimated attributable mortality rate between 5-13%<sup>11</sup>. Although the incidence and mortality rates have decreased with the development of preventive strategies, VAP remains the most common cause of nosocomial infection in ICUs. Current challenges in the management of VAP include the lack of a gold standard for diagnosis, the absence of effective preventive strategies and the rise of microbial resistance<sup>12</sup>. Sars-Cov-2 patients are particularly at risk of developing VAP; indeed several studies have shown that the average duration of mechanical ventilation is longer in COVID 19 Acute Respiratory Distress Syndrome (ARDS) compared to “classic” ARDS<sup>13,14</sup>. However, the incidence of nosocomial pneumonia in this population remains unclear with numbers ranging between 23% to 50%<sup>15,16</sup>. Risk factors for VAP have been studied in the ICU population but there is little data concerning the COVID-19 ICU population. Dexamethasone has emerged as a cornerstone treatment for oxygen-requiring Sars-Cov-2 patients as it is the first drug having consistently shown a decrease in mortality<sup>17</sup>. On the other hand, corticosteroids have been associated with immunosuppression and subsequent superinfections in non COVID ICU patients<sup>18</sup>. The impact of wide-use systemic corticosteroid therapy and immunomodulating drugs on VAP in a COVID-19 setting has yet to be fully understood. It stands to reason that further exploring the characteristics of VAP in a COVID 19 setting is the

first step to reducing its incidence and improving the outcome of mechanically-ventilated patients.

## **MATERIELS AND METHODS**

### **Setting and study design**

This study was conducted to analyze the incidence and risk factors for ventilation-acquired pneumonia in COVID-19 patients during the first year of the pandemic in Marseille, France. A retrospective analysis of prospectively collected data of 248 adult patients with severe COVID-19 admitted to seven ICUs of three tertiary public hospitals between March 2020 to November 2020 was performed. 87 patients who were never exposed to invasive mechanical ventilation were excluded, leaving 161 mechanically ventilated patients left as our final cohort. We then distinguished all 82 patients who developed at least one ventilation-acquired pneumonia during their ICU stay and proceeded to describe the incidence and characteristics of this group. Secondly, a control group constituted of the remaining 79 patients allowed us to search for potential VAP risk factors (Fig 1).

The participating centers shared similar preventive care methods concerning hospital acquired infections including VAP bundles. No selective digestive decontamination was used and stress ulcer prophylaxis were applied when indicated.

All consecutive patients with a Sars-CoV-2 infection diagnosis and admitted to the participating ICUs during the study period were included. Exclusion criteria were : Age < 18 years, admission to ICU for other reasons than COVID-19, and no exposure to mechanical ventilation.

### **Diagnosis and definitions**

The COVID-19 infection diagnostic was obtained through polymerase chain reaction (PCR) nasal or tracheo-bronchial swabs at admission depending on whether or not the patient was under mechanical ventilation. Nucleic acids were extracted using the EZ1 Virus Mini Kit v2.0 (Qiagen®, Courtaboeuf, France) and the two RT-PCR assays were carried out using the LightCycler Multiplex RNA Virus Master kit (Roche Diagnostics®, Mannheim, Germany) as previously described.

In a few cases of negative PCR swabs contrasting with strong clinical, radiological and anamnestic evidence, Sars-Cov-2 infection diagnosis was also given.

Concerning ventilation-acquired pneumonia in this study, the diagnosis was obtained by the combination of two criteria: (1) clinical, biological and radiological signs leading the practitioner to suspect an infection and prescribe an antibiotic treatment, (2) a positive

respiratory microbiologic isolate. These criteria follow the latest European center for disease control's definition for VAP<sup>19</sup>.

Infections were considered ICU acquired infections if they occurred  $\geq 48$ h from ICU admission. VAP was classified into early versus late whether it occurred  $< 5$  days or  $\geq 5$  days from the start of mechanical ventilation.

### **Collected data**

The following patient data were collected at admission: age, sex, BMI, comorbidities including diabetes, hypertension, cardiovascular disease, metabolic syndrome, active smoking, chronic lung disease, chronic kidney disease, immunocompromised status. Patient characteristics at ICU admission included severity scores, PaO<sub>2</sub>/FiO<sub>2</sub> ratio and biological inflammation markers. Three critical patient severity scores were collected: "*Index de Gravité Simplifié 2*" (IGS 2), Charlson, and ROX. These scores are complementary in describing patient gravity, the first two estimate predicted hospital mortality using patient characteristics within the first 24H of ICU admission and patient comorbidities respectively. The ROX score, recently developed, is a tool for predicting high-flow nasal cannula failure and the need for mechanical ventilation.

New prognostic biomarkers including Neutrophil to lymphocyte ratio (NLR) and Systemic immune-inflammation index (SII) have been studied in recent years as potential tools for sepsis management<sup>20</sup> as well as COVID-19 prognosis<sup>21</sup> and were also collected for analysis. Infected patients within the first 48h of ICU admission were also reported.

We also described infectious related therapies used before and during early ICU stay such as corticosteroids, immunomodulating drugs (anti IL-6, anti IL-1, Jakavi, Lopinavir/Ritonavir), hydroxychloroquine and antibiotics.

ICU patient management, complications and outcome were collected. Respiratory treatments such as high-flow nasal cannula (HFNC) and non-invasive ventilation (NIV) usage, prone positioning, use of neuromuscular blockers (NMB), the need for Extracorporeal membrane oxygenation (ECMO) as well as high-dose corticosteroid therapy were reported. Other organ failures and support systems such as septic shock and norepinephrine use, acute renal failure and renal replacement therapy (RRT) were documented. Median ventilation duration, hospital and ICU length of stay (LOS) and mortality rates were also reported.

## Microbiological investigations

The bacteriologic diagnostic was obtained by quantitative culture using a positive threshold of  $10^5$  and  $10^2$  Colony Forming Units (CFU/ml) for endotracheal aspirates and BAL fluids, respectively. Cultures were considered as polymicrobial if >2 microorganisms grew. Isolates were identified using Matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) with a log score >1.9 as previously described. Antibiotic susceptibility testing was performed using disk diffusion method according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and minimum inhibitory concentrations (MICs) were obtained using the E-test method (Biomérieux, Marcy l'Etoile, France).

Among enterobacteria, extended spectrum beta-lactamase producers (ESBL) were identified when a synergy between ceftriaxone and clavulanate was observed. Other enterobacteria resistant to ceftriaxone were considered as AmpC-hyper producers (CASEH). We also screened for methicillin-resistant *Staphylococcus aureus* (MRSA) and *Stenotrophomonas maltophilia* resistant isolates.

*Herpesviridae* (Herpes simplex, cytomegalovirus and Epstein-Barr virus) were reported but were considered to be reactivations and not considered a component of VAP. We also screened for evidence of invasive pulmonary aspergillosis (IPA), as there are now several case reports of this affecting COVID-19 patients<sup>22</sup>.

Viral reactivations (HSV and CMV) as well as median Ct Sars-Cov-2 viral loads and length of PCR positivity were also documented.

## Statistical analysis

Descriptive statistics were produced for demographic, clinical, and laboratory characteristics of patients. Mean, median and interquartile range [IQR] are reported for continuous variables, and numbers and percentages are reported for categorical variables. Groups were compared with unpaired t-test or Mann-Whitney nonparametric tests, according to data distribution, for continuous variables and with chi-square test (or Fisher exact test when appropriate) for categorical variables.

The most relevant risk factors associated with VAP were identified by univariate logistic regression analysis. Variables with a p-value of less than 0.2 in univariate analysis were included in the final multivariable logistic regression model. Odds ratios (ORs) and 95% CIs

are presented. SPSS version 20.0 software (IBM, Armonk, New York) was used for all statistical analyses. A p-value of  $< 0.05$  was regarded as statistically significant.

### **Ethical statement**

This study was approved by the local Ethics Commission (2020-53) and the French Society of Anesthesia and Critical Care (00010254-2020-262). According to French law, the informed consent was not required due to the design of the study.

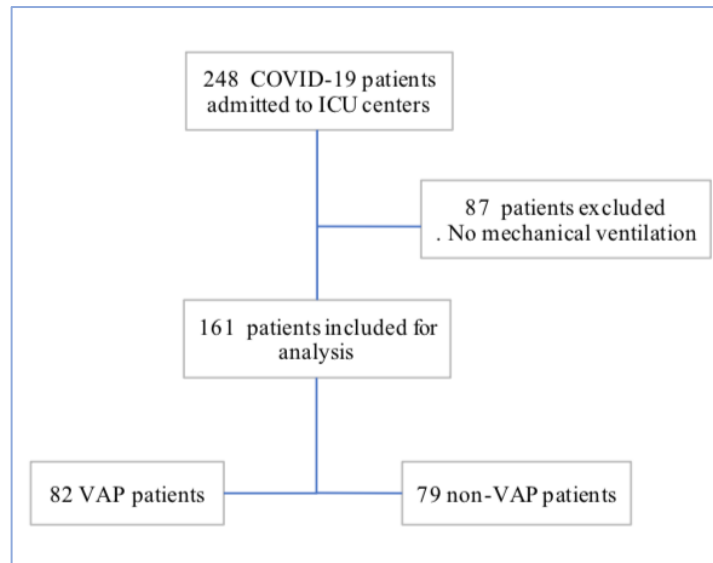
## RESULTS

### Patient characteristics

82/161 (51%) patients developed at least one ventilation-acquired pneumonia during ICU stay. VAP patient clinical characteristics are summarized in Table 1. Median age was significantly slightly higher in this population at 65 years compared to 62 years in the non VAP group ( $p = 0,02$ ). 83% were men and the average Body Mass Index (BMI) was  $27,7\text{kg/m}^2$  (25,3-32,1) with 32% of obese patients. 91% of VAP patients had at least one comorbidity, the most frequent being high blood pressure and diabetes, present in 45/82 patients (55%) and 25/82 patients (30%) respectively. Comorbidities were similar in VAP and non VAP groups. Active smoking was rare in our study, reported at 6%.

Table 1 also reported patient status at ICU admission. This predictor scored significantly worse in the ventilation-acquired pneumoniae cohort compared to the control group (3,7 vs 5,8;  $p = 0,012$ ). Biological markers such as ferritin, fibrinogen, D-dimer levels were similar in both groups however, C -reactive protein serum levels were higher in VAP patients (185mg/L vs 98mg/L;  $p = 0,03$ ). Both of these parameters were significantly higher in the VAP group ( $p = 0,016$ ). 13/82 patients were infected within the first 48h of ICU admission (16%), with an equal percentage found in the non-VAP group. Percentage of CT scan lung lesions at ICU admission were also statistically more important in VAP patients with an average of 37% of damaged lung compared to 27% in the control group ( $p = 0,038$ ). Delay between conventional hospitalization and ICU admission was short, with patients being transferred to the ICU at day 0 in the VAP group versus day 1 in non-VAP patients, however this difference was not statistically significant.

**Figure 1: Study Flow chart**



**Table 1: Patient clinical and biological characteristics**

Variable	All patients N = 161	VAP patients N = 82 (51%)	Non VAP patients N = 79 (49%)	P - value	OR (95% CI)
Age - YEAR, median (IQR)	63 (57-72)	65 (58-73)	62 (54-69)	0,02	1,03 (1,00-1,06)
Sex - Male (%)	124 (77)	68 (82,9)	56 (70,9)	0,069	
BMI Kg/m <sup>2</sup> , median (IQR)	28 (25-32)	27,7 (25,3-32,1)	28 (25,8-33,8)	0,51	0,98 (0,93-1,03)
18-24,9	31 (19)	16 (23,2)	15 (21,4)	0,8	
25-29,9	52 (32)	27 (39,1)	25 (35,7)	0,67	
30-40	49 (30)	23 (33,3)	26 (37,1)	0,63	
> 40	7 (4)	3 (3,9)	4 (5,3)	0,71	
<b>Comorbidities</b>	147 (91,3)	75 (91,5)	72 (91,1)		
Hypertension	88 (54)	45 (54,9)	43 (54,4)	0,95	1,01 (0,54-1,89)
Diabetes	58 (36)	25 (30,5)	33 (41,8)	0,13	0,61 (0,32-1,17)
Cardiovascular disease	31 (19)	19 (23,2)	12 (15,2)	0,2	1,68 (0,75-3,74)
<i>Coronary disease</i>	20 (12,4)	11 (13,4)	9 (11,4)	0,69	
<i>Chronic heart failure</i>	3 (1,9)	1 (1,2)	2 (2,5)	0,61	
<i>Occlusive arteriopathy</i>	4 (2,5)	3 (3,7)	1 (1,3)	0,62	
Metabolic syndrome	36 (22,4)	16 (19,5)	20 (25,3)	0,37	
Current smoking	6 (3,7)	5 (6,1)	1 (1,3)	0,14	5,06 (0,57-44,3)
Chronic lung disease	39 (24)	20 (24,4)	19 (24,1)	0,96	1,01 (0,49-2,09)
<i>Obstructive sleep apnea</i>	21 (13)	11 (13,4)	10 (12,7)	0,88	
Chronic kidney disease	12 (7,5)	4 (4,9)	8 (10,1)	0,21	0,45 (0,13-1,57)
Immunocompromised*	20 (12,4)	11 (13,4)	9 (11,4)	0,69	1,2 (0,47-3,08)
Chronic treatment	103 (64)	52 (63,4)	51 (64,6)	0,88	0,95 (0,5-1,81)
<b>Status at ICU admission</b>					
Delay between hospitalisation and ICU, d	0 (1-3)	0 (0-1,25)	1 (0-4)	0,12	
IGS2	35 (28-43)	34 (30-43)	35 (27-43)	0,86	
CHARLSON	3 (1-4)	3 (2-4)	2 (1-4)	0,1	
SOFA	4 (3-7)	4 (3-7)	4 (2-7)	0,43	
ROX	4,6 (3-9,3)	3,7 (3-7)	5,8 (3-10,1)	0,012	
PaO <sub>2</sub> /F <sub>i</sub> O <sub>2</sub> ratio (mmHg)	131 (96-180)	132,5 (91,5-179)	130 (100-181,5)	0,42	0,99 (0,99-1)
Maximum Temperature (°C)	38,3 (37,5-39)	38,3 (37,6-38,7)	38,4 (37,3-39)	0,7	0,93 (0,67-1,31)
Neutrophil to lymphocyte ratio	7,3 (5,1-13)	8,3 (5,5-15,6)	6 (4,6-9,2)	0,016	
Systemic immune-inflammation index (SII)	1610 (971-3270)	2113 (1116-3900)	1281 (834-2054)	0,016	1,11 (1,01-1,2)
Ferritin (µg/L)	1427 (1013-2345)	1241 (796-1611)	2273 (976-4141)	0,19	
Fibrinogen (g/L)	6,6 (5,9-7,7)	6,7 (5,9-8)	6,6 (5,7-7,3)	0,59	
D-dimer (µg/L)	1,5 (1-4)	1,5 (0,8-4)	1,6 (1,1-2,9)	0,9	
Procalcitonin (ng/mL)	0,3 (0,19-0,58)	0,3 (0,2-0,5)	0,3 (0,2-1,3)	0,49	
C-reactive protein (mg/dL)	170 (91,6-227)	185,9 (120-251)	98,7 (83,6-184)	0,03	0,89 (0,64-1,23)
Infection within 48h of ICU admission	26 (16,1)	13 (15,9)	13 (16,5)	0,91	
CT scan lung lesion (%)	31,2	37,3	27,8	0,038	

Data throughout Table 1-5 are presented as No. (%) of the included patients or median (interquartile range)

\* : includes solid tumors, active hematologic cancers, transplantation, HIV, immunosuppressive treatment



## Infectious disease management

Table 2 summarizes anti infectious drug-based therapies used before and during ICU stay. VAP patients received antibiotics before ICU in half of the cases (47%) which is significantly lower than in non VAP patients (65%;  $p = 0,024$ ), with a median treatment duration of 3 days before ICU (IQR, 2-5). Hydroxychloroquine use was similar in both groups, prescribed in about 30% of patients in pre-ICU and early ICU settings. Antibiotic usage rate during the first 2 days of ICU rose to 83% in VAP patients, with broad spectrum antibiotics predominantly used (ie, 3rd generation cephalosporins, Fluoroquinolones,  $\beta$ -lactam and  $\beta$ -lactam inhibitors, carbapenems, aminosides, anti MRSA). Dexamethasone 6mg per day was used in 31/82 (38%) VAP patients and 20/79 (25%) non VAP patients ( $p = 0,09$ ) with a global incidence of 31% when analyzing our 161 ventilated patients. Immunomodulating drugs were used in 33% of VAP patients and in 21% of non VAP patients ( $p = 0,1$ ).

**Table 2: Anti-infective therapies**

Variable	All patients N = 161	VAP patients N = 82 (51%)	Non VAP patients N = 79 (49%)	P - value	OR (95% CI)
<b>Early ICU management</b>					
Antibiotic treatment within 48h of ICU admission	137 (85,6)	68 (82,9)	69 (88,5)	0,32	
<b>Corticosteroids</b>					
<i>Dexamethasone 6mg</i>	51 (31,7)	31 (37,8)	20 (25,3)	0,09	1,8 (0,9-3,5)
<i>Median duration of dexamethasone 6mg</i>	10 (7-10)	10 (7-10)	10 (6-10)	0,22	
<b>Immunomodulators</b>					
44 (27,3)	27 (32,9)	17 (21,5)	0,1		
<i>Anakinra (anti IL-1)</i>	19 (11,8)	10 (12,2)	9 (11,4)	0,87	
<i>Tocilizumab (anti IL-6)</i>	4 (2,5)	1 (1,2)	3 (3,8)	0,31	
<i>Ruxolitinib (Jakavi)</i>	19 (11,8)	12 (14,6)	7 (8,9)	0,26	
<i>Lopinavir/Ritonavir</i>	18 (11,2)	13 (15,9)	5 (6,3)	0,063	
Hydroxychloroquine	107 (66,5)	50 (61)	57 (72)	0,13	
<b>Pre ICU management</b>					
Antibiotic treatment	90 (56,3)	39 (47,6)	51 (65,4)	0,024	0,48 (0,25-0,91)
<i>3rd generation cephalosporin</i>	60 (37,2)	25 (30)	35 (44)	0,069	
<i>Azithromycin</i>	60 (37,2)	24 (29)	36 (45,5)	0,035	
<i>Penicillin A +/- Clavulanic acid</i>	20 (12,4)	9 (10,9)	11 (13,9)	0,57	
<i>Piperacillin - Tazobactam</i>	11 (6,8)	6 (7,3)	5 (6,3)	0,8	
Duration of pre ICU antibiotic treatment, d (IQR)	4 (2-5)	3 (2-5)	4 (2-5,5)	0,16	
Hydroxychloroquine	52 (32)	23 (28)	29 (36,7)	0,24	
Dexamethasone 6mg	8 (5)	3 (3)	5 (6,3)	0,48	

## Patient management, complications and outcome during ICU stay

Information about patient respiratory management and other ICU specific therapies as well as complications are detailed in Table 3. Non-invasive respiratory support consisted in high-flow nasal cannula and non-invasive ventilation, used respectively in 63% and 28% of VAP patients. There was no difference in the usage rate of these treatments between both groups. Over 90% of patients, regardless of the group, required neuromuscular blockers whereas 13/82 VAP patients (16%) required extra corporeal membrane oxygenation (ECMO) support. Nitric oxide was used twice as often in the VAP group as opposed to the control group ( $p = 0,004$ ). High dose solumedrol treatment was statistically associated with VAP ( $p = 0,006$ ). Although norepinephrine was more frequently used in VAP patients ( $p = 0,001$ ), there was no difference in incidence of septic shock or acute renal failure between both groups. Pneumothorax and cardiac rhythm disorders were also more frequently diagnosed in VAP patients. Duration of COVID-19 PCR positivity was 13 days in the VAP group and 11 days in the non-VAP group ( $p = 0,2$ ). ICU LOS, hospital LOS and days under mechanical ventilation were all significantly longer in VAP patients ( $p < 0,001$ ). A 25% mortality rate was reported and was not different between groups.

**Table 3:** ICU management and outcome

Variable	All patients N = 161	VAP patients N = 82 (51%)	Non VAP patients N = 79 (49%)	P - value	OR (95% CI)
<b>Respiratory management</b>					
Treated with High-flow nasal cannula (HFNC)	105 (65,2)	52 (63,4)	53 (67,1)	0,62	0,85 (0,44-1,6)
Treated with Non-invasive ventilation (NIV)	43 (26,7)	23 (28)	20 (25,3)	0,69	1,15 (0,57-2,3)
Neuromuscular blockers (NMB)	152 (94,4)	79 (96,3)	73 (92,4)	0,32	
Prone position	132 (82)	72 (87,8)	60 (75,9)	0,05	
Nitric oxide (NO)	52 (32)	35 (42,6)	17 (21,5)	0,004	
Extracorporeal membrane oxygenation (ECMO)	24 (14,9)	13 (15,9)	11 (13,9)	0,73	
Solumedrol 2mg/kg	21 (13)	17 (20,7)	4 (5,1)	0,006	4,9 (1,5-15,3)
<b>ICU complications and outcome</b>					
Norepinephrin > 1mg/h	82 (50,9)	52 (63,4)	30 (37,9)	0,001	
Septic shock	50 (31)	30 (36,6)	20 (25,3)	0,12	
Blood stream infections	40 (25,5)	32 (80)	8 (20)	< 0,001	
Acute renal failure	76 (47,5)	43 (52,4)	33 (42,3)	0,2	
Renal replacement therapy	24 (14,9)	13 (15,9)	11 (13,9)	0,73	
Pneumothorax	11 (6,9)	10 (12,2)	1 (1,3)	0,006	
Rythm disorders	39 (24,2)	30 (36,6)	9 (11,4)	< 0,001	
Conduction disorders	14 (8,7)	10 (12,2)	4 (5,1)	0,108	
HSV-1 reactivation	19 (11,8)	13 (15,9)	6 (7,6)	0,104	
CMV reactivation	18 (11,2)	13 (15,9)	5 (6,3)	0,055	
Sars-Cov 2 viral loads (Ct/mL)	28,9 (24,9-31,7)	29,7 (24,8-32)	28 (24,9-31)	0,38	1,03 (0,96-1,10)
Duration of PCR positivity, d	12 (6,5-17)	13 (8-17)	11 (5,7-17)	0,2	1,02 (0,98-1,07)
Delay between ICU and IMV	0 (0-1,5)	0 (0-2)	1 (0-1)	0,2	
IMV duration, d	18 (8,2-33)	31,5 (15-47,2)	10 (5-18,2)	< 0,001	
Length of stay - ICU, d	24,5 (15-43)	39,5 (21-57)	17 (8-25)	< 0,001	
Length of stay - Hospital, d	35 (21-50)	43 (30-62,5)	24 (14-37,5)	< 0,001	
Death during ICU stay	41 (25,5)	21 (25,6)	20 (25,3)	0,96	

## VAP characteristics and bacterial documentation

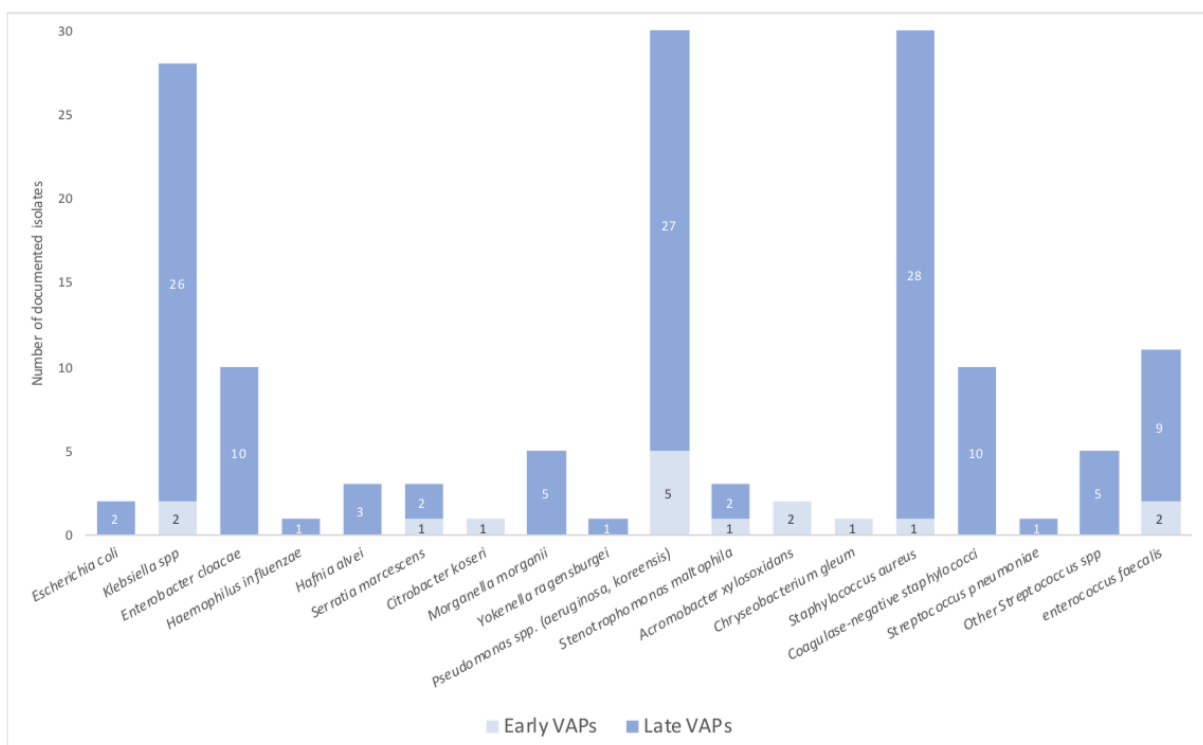
The type and incidence of each bacteria responsible for VAP is detailed in Table 4. These infections were categorized into early and late VAP, on whether they occurred before or after the 5<sup>th</sup> day of mechanical ventilation. 72 patients (88%) developed late VAPs with a median delay of 10 days after intubation (IQR; 7-17). 31% of VAP were due to multi-drug resistant bacteria (MDR) with no significant difference between early and late infections. VAP associated blood stream infections (BSI) were exclusively documented in late VAPs (20/72), with 33% caused by MDR bacteria.

Regardless of the delay of VAP occurrence, three organisms were responsible for 60% of infections; *Klebsiella spp*, *Pseudomonas spp* and *Staphylococcus aureus*. Gram negative species were predominantly involved in 62% of VAPs. When analyzing the different types of bacteria between both VAP groups, we noticed that *Staphylococcus aureus* was mainly documented in late VAP with an incidence of 22% vs only 6% in early VAP, however this difference was not statistically significant ( $p = 0,08$ ). Most of the strains were Methicillin – sensitive with only 5/29 isolates being Methicillin-resistant *Staphylococcus aureus*, these resistant strains all being recorded in late VAP. There were no differences between both groups concerning other bacteria species involved in VAP except for *Acromobacter xylosoxidans* which was predominantly found in early VAP ( $p = 0,005$ ). There were no recorded cases of invasive pulmonary aspergillosis in this study.

**Table 4: Ventilation-acquired pneumonia characteristics and bacterial documentation**

Variable	All VAPs N = 82	Early VAPs N = 10	Late VAPs N = 72	P - value
Average delay of VAPs, d	9 (6-14)	3 (3-3)	10 (7-17)	< 0,001
Polymicrobial VAPs (> 2 isolates)	15 (18)	2 (20)	13 (18)	1
Multi-drug resistant (MDR) VAPs	26 (31,7)	2 (20)	24 (33)	0,49
VAP associated blood stream infections (BSI)	20 (24)	-	20 (27,7)	
VAP associated MDR BSIs	8 (33)		8 (33)	
<b>Documented microbiological isolates</b>	<b>N = 148</b>	<b>N = 16</b>	<b>N= 132</b>	
<b>Gram negative bacteria (%)</b>	<b>(62)</b>	<b>(81)</b>	<b>(59)</b>	
<b>Fermenters</b>				
<i>Escherichia coli</i>	2		2 (2,7)	1
<i>Klebsiella spp</i>	28 (18,7)	2 (12)	26 (19)	0,87
<i>Enterobacter cloacae</i>	10 (6,7)		10 (7)	0,45
<i>Haemophilus influenzae</i>	1		1 (0,7)	1
<i>Hafnia alvei</i>	3		3 (2,2)	1
<i>Serratia marcescens</i>	3	1 (6)	2 (2,7)	0,8
<i>Citrobacter koseri</i>	1	1 (6)		0,24
<i>Morganella morganii</i>	5		5 (3,7)	0,87
<i>Yokenella ragenburgei</i>	1		1 (0,7)	1
<b>Non fermenters</b>				
<i>Pseudomonas spp. (aeruginosa, koreensis)</i>	32 (21,4)	5 (31)	27 (20)	0,67
<i>Stenotrophomonas maltophila</i>	3	1 (10)	2 (2,7)	0,8
<i>Acromobacter xylosoxidans</i>	2	2 (12)		0,005
<i>Chryseobacterium gleum</i>	1	1 (6)		0,24
<b>Gram positive bacteria (%)</b>	<b>(38)</b>	<b>(19)</b>	<b>(41)</b>	
<i>Staphylococcus aureus</i>	29 (20)	1 (6)	29 (22)	0,08
Methicillin-sensitive <i>Staphylococcus aureus</i>	24	1	23	0,68
Methicillin-resistant <i>Staphylococcus aureus</i>	5		5	0,76
<i>Coagulase-negative staphylococci</i>	10 (6,7)		10 (7)	0,45
<i>Streptococcus pneumoniae</i>	1		1 (0,7)	1
Other <i>Streptococcus spp</i>	5		5 (3,7)	1
<i>Enterococcus faecalis</i>	11 (7,4)	2 (12)	9 (6,7)	0,87

**Figure 2: Ventilation-acquired pneumonia bacterial documentation**

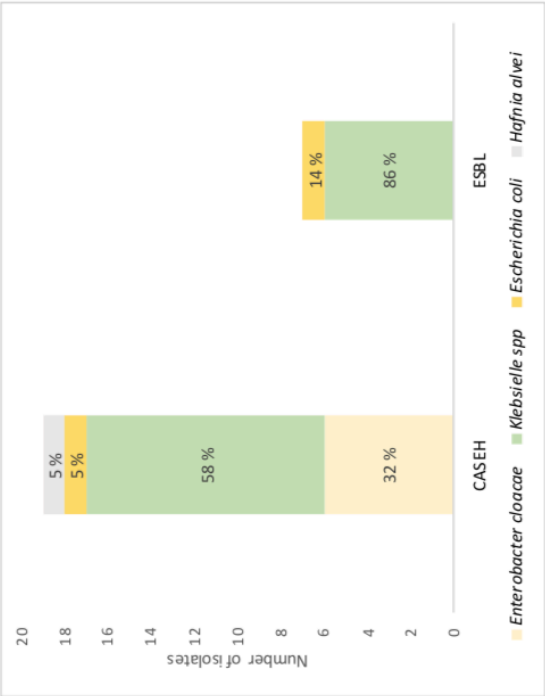
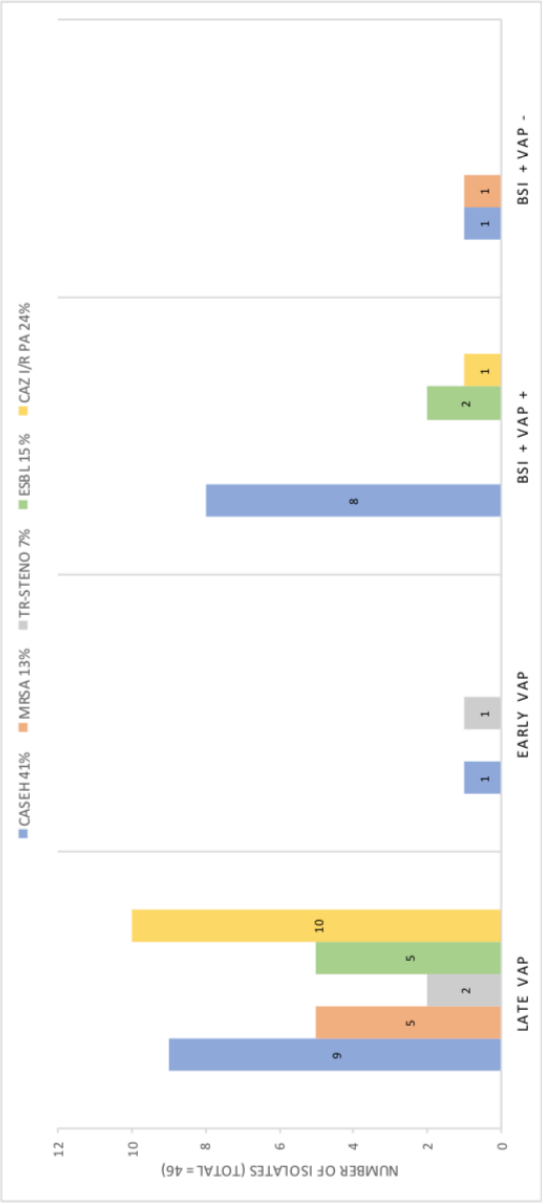


## **Antibiotic resistance mechanisms**

Finally, we analyzed the different types of antibiotic resistance mechanisms within VAP and BSI MDR infections(Figure 3). These infections occurred in 26% of patients who experienced at least one infection during ICU stay and in 17% of our ventilated cohort. The dominant resistance mechanisms were cephalosporinase hyper-production (CASEH), Ceftazidime resistant *Pseudomonas aeruginosa* (CAZ I/R PA) and extended-spectrum beta-lactamase (ESBL) with respective incidences of 41%, 24% and 15%. Methicillin-resistant *Staphylococcus aureus* was documented in 6/46 isolates. Early VAP and VAP-free blood stream infections accounted for 4/46 BMR infections (9%) in our ventilated patients, while late VAP accounted for 67%.

*Klebsiella spp (pneumoniae, aerogenes)* was the predominant bacteria group responsible for CASEH and ESBL resistance mechanisms with incidences of 58% and 86% respectively. Other Enterobacteriaceae species involved were *Enterobacter cloacae*, *Escherichia coli* and *Hafnia alvei*.

Figure 3: Antibiotic resistance mechanisms according to type of infection and bacteria



## Multivariate analysis

In this multivariate analysis (Table 5), we singled-out clinically relevant factors that had a univariate p score < 0,2 in order to identify potential VAP risk factors. Age and male sex were associated to VAP (p = 0,014 and 0,018 respectively). IGS 2 and ROX scores at admission were associated to VAP with paradoxically higher IGS 2 scores having a protective effect. Dexamethasone was significantly associated to VAP (p = 0,046) with an odds ratio at 3,2 (1,01-10). As in the univariate analysis, pre-ICU antibiotic treatment, was strongly correlated to VAP incidence as a protective factor [p = 0,009; OR=0,23 (0,07-0,7)]. Neutrophil to lymphocyte ratio was no longer associated to VAP in the multivariate analysis.

**Tableau 5:** Multivariate risk factors associated with VAPs

Variable	VAP patients N = 82 (51%)	Non VAP patients N = 79 (49%)	OR (95% CI)	Multivariate adjusted P-value
Age - YEAR, median	65 (58-73)	62 (54-69)	1,08 (1,01 - 1,15)	0,014
Sex - Male	34 (30-43)	35 (27-43)	3,99 (1,26 - 12,6)	0,018
IGS 2	34 (30-43)	35 (27-43)	0,94 (0,89 - 0,99)	0,037
CHARLSON	3 (2-4)	2 (1-4)	1,19 (0,79 - 1,78)	0,39
ROX	3,7 (3-7)	5,8 (3-10,1)	0,85 (0,75 - 0,97)	0,015
Dexamethasone 6mg	31 (37,8)	20 (25,3)	3,2 (1,01 - 10)	0,046
Immunomodulators	27 (32,9)	17 (21,5)	2,73 (0,84 - 8,8)	0,092
Pre ICU antibiotic treatment	39 (47,6)	51 (65,4)	0,23 (0,07 - 0,7)	0,009
Neutrophil Lymphocyte ratio	8,3 (5,5-15,6)	6 (4,6-9,2)	0,99 (0,95 - 1,03)	0,82
Duration of PCR positivity, d	13 (8-17)	11 (5,7-17)	1,02 (0,96 - 1,08)	0,41
Delay between hospitalisation and ICU, d	0 (0-1,25)	1 (0-4)	0,96 (0,79 - 1,16)	0,7
Delay between ICU and IMV, d	0 (0-2)	1 (0-1)	1,18 (0,92 - 1,51)	0,18

## DISCUSSION

### Ventilation-Acquired Pneumonia characteristics

The studied population was predominantly comorbid males (83%) with high blood pressure and diabetes as the two most described comorbidities. This strengthens the already common knowledge that Sars-Cov-2 is most virulent in these types of patients<sup>23</sup>. Time between ICU admission to intubation was very short with a median intubation date at day 1 reflecting the critical level of respiratory failure these patients faced. Our work provides a detailed description of VAP microbiological distribution. Infections occurred at day 3 (IQR, 3-3) for early VAP and day 9 (6-14) for late VAPs. The proportion between early and late onset VAP in this study, with a majority of late VAP (88%) is in line with other reports. Most infections were caused by Gram negative bacteria (62%) with *Pseudomonas aeruginosa* being the most documented bacteria (21%). These numbers are similar to the ones published by Grasselli et al<sup>24</sup>. Staphylococcus aureus was predominantly found in late VAP ( $p = 0,08$ ) contrasting with the distribution of Gram-positive bacteria in VAP settings which are usually found in the early stages. However this could simply be explained by a lack of power from low early VAP incidence.

Another key finding with potentially important clinical implications is that MDR bacteria caused about one third of VAPs. The most common antibiotic resistance mechanism was AmpC cephalosporin hyperproduction (CASEH) found in 90% of the cases in either *Klebsiella* or *Enterobacter spp.* MRSA strains represented 17% of all staphylococcus aureus VAP, remaining low and in accordance with previous studies. This high proportion of MDR infections could be explained by a large number of patients (47%) receiving pre-ICU broad spectrum antibiotics including 3<sup>rd</sup> generation cephalosporins. Furthermore, the surge of critically-ill patients during the pandemic might have influenced the quality of critical care provided by overloading medical staff potentially increasing the risk of ventilation-associated lower respiratory tract infections (VA-LRTI) by MDR bacteria. Indeed, previous studies reported that contact isolation measures, especially inappropriate glove use, could increase the transmission of MDR bacteria<sup>25</sup>.



## **Ventilation-Acquired Pneumonia risk factors**

Age and sex were the two demographic characteristics associated to VAP in our multivariate analysis. Age has widely been recognized as a risk factor for nosocomial infection and VAP in COVID and non-COVID settings. Various mechanisms such as decreased immune function, frequent chronic illnesses and malnutrition explain why older patients are more likely to develop hospital-acquired infections like VAP<sup>24,26</sup>. Male sex has been associated to VAP in non-COVID literature<sup>27</sup> but to our knowledge this study is the first to report such findings in a COVID cohort. However, the Sars-Cov-2 itself could be a confounding factor as we know that this virus is more virulent in men, responsible for higher ICU admission and mortality rates compared to women<sup>28</sup>.

The ROX score, recently developed, has been used during the COVID-19 pandemic by certain teams to predict the need for invasive mechanical ventilation after high-flow nasal cannula failure<sup>29</sup>. This clinical score (SpO<sub>2</sub>/FiO<sub>2</sub>/RR) was the only score associated to VAP incidence and may reflect that the level of acute respiratory failure before intubation could be associated to the development of VA-LRTI.

The role of dexamethasone's impact on ventilator-acquired pneumonia was a key question in this study. This treatment at a dose of 6mg per day during 10 days is a pivotal treatment for severe cases of COVID-19 infection, as it is the only treatment having demonstrated a decrease in ICU mortality<sup>17</sup>. However, the impact of this treatment on VAP incidence in Sars-COV-2 infected patients is still up for debate, with contrasting reports in the last two years. Reys et al. in a prospective study revealed that dexamethasone was a risk factor for ICU-acquired respiratory tract infections whereas Gragueb-Chatti et al. found no relation between VAP or BSI and dexamethasone<sup>30,31</sup>. In our study, the multivariate analysis revealed that Dexamethasone was associated with ventilation-acquired pneumonia with an odds ratio of 3,2 (1,01-10). Other corticosteroid treatments were used such as high-dose solumedrol, which had a higher incidence in the VAP group; however, this treatment was in a majority of cases started after VAP diagnosis and is the reason why it is difficult to consider it as a potential risk factor. Dexamethasone's purpose is to mitigate inflammation-related organ injuries. ICU patients with low biological markers at admission could be a sub-group of patients in which dexamethasone favors bacterial superinfections rather than treats inflammation lesions. Faced with these many contradicting results, further prospective studies are needed to confirm this potential unintended effect.

Our multivariate analysis revealed that pre-ICU antibiotic treatment was associated with a reduction in VAP incidence (see Table 5). Based on our definition of VAP, high antibiotic exposure prior to bacterial samplings might have caused falsely negative results leading to unaccounted non documented VAP. Respiratory bacterial co-infection rates during standard hospitalization in COVID 19 are low<sup>32,33</sup> and this was also the case in our study. The impact of inadequate probabilistic antibiotic treatment on the rise of antibiotic resistance has been an ongoing and growing global health issue<sup>12</sup>. Coupling this to the low evidence level of results obtained from our retrospective study, it seems unreasonable to advocate for pre-emptive antibiotic treatment before ICU admission with the objective of reducing VAP incidence in COVID-19. On the other hand, recent ICU healthcare-associated pneumonia (HCAP) recommendations state that systemic prophylactic antibiotics, through selective digestive decontamination, may help reduce HCAP incidence<sup>34</sup>. Future prospective studies are needed to clarify the use and timing of prophylactic antibiotics.

Neutrophil to lymphocyte ratio at ICU admission was associated to VAP in the univariate analysis but no longer in the multivariate analysis. NLR has been used in these last years as a marker for endothelial dysfunction, a mechanism particularly present in COVID 19 pathogenesis. Different studies found associations between this biological marker and poor clinical outcome, with Jimeno et al. demonstrating a relation between peak NLR and death<sup>35</sup>. However, NLR lacks specificity and works linking it to prognostication of sepsis and oncological diseases make it difficult to use on a practical basis. Disease-specific thresholds may increase the reliability of this marker and could be a focal point of future studies.

### **Incidence of Ventilation-Acquired Pneumonia**

In this retrospective study, we analyzed the epidemiologic and etiologic factors influencing the development of ventilation-acquired pneumonia in a cohort of critically ill COVID-19 patients. The incidence of VAP in this study was 51%, which is in line with other reported results ranging between 44% to 64%<sup>36,37</sup>. This contrasts with VAP occurrence in non-COVID ICU settings which seem to have lower incidence rates (13% - 29%)<sup>16,27</sup>. One of the recurrent explanations mentioned by different studies is the longer duration of mechanical ventilation in Sars-Cov-2 related ARDS compared to other types of ARDS. In our study, the median duration of mechanical ventilation was 18 days (IQR, 8,2-33) which is slightly longer than other reports (13-15 days). This could be due to the fact that this study analyzes the earliest period of the

COVID 19 pandemic, a time in which intensivists were encouraged to intubate patients at early stages. Also, SARS-Cov-2 infection has a nervous tissue tropism and is associated with confusion agitation and encephalopathy<sup>38</sup>, making these patients more difficult to wean from mechanical ventilation. On a cellular level, one of the strongest predictors of nosocomial infection in critically-ill patients is impaired immune cell function. Patients with COVID-19, in keeping with other critical illness syndromes such as bacterial sepsis and major trauma, experience a complex dysregulation of their immune function with features of both hyperinflammatory activation and organ damage as well as impaired antimicrobial functions. Notably, damage to the alveolar membrane, although not specific to COVID-19, may facilitate invasion of bacterial species<sup>39</sup>, similarly to Influenza infection. However, when comparing VAP incidences in a COVID versus influenza ICU population, these remained significantly higher in the COVID 19 cohort (50% vs 30%)<sup>40</sup>. A reason for this could be widespread thrombosis which distinguishes the pulmonary pathophysiology of Covid-19 from that of equally severe influenza virus infection. These lesions might promote local immunity alteration, bacterial colonization, and further lung infection. However, further studies are required to confirm this hypothesis.

### **Limitations**

We noted several limitations to our study. First of all, it is a retrospective analysis and therefore subject to interpretative bias. Both, the low incidence of dexamethasone and the rather high incidence of immunomodulating drugs are not representative of updated ICU COVID-19 management guidelines and weaken the generalization of our results. Blood stream infections were predominantly VAP associated (80%) which made it impossible to analyze their association to dexamethasone. Immunomodulators were used at a Future large multicentric studies are needed to help clarify both the impact of dexamethasone and the role of prophylactic antibiotics in Sars-Cov-2 patients in order to optimize patient care.

## **CONCLUSION**

In this retrospective study, we analyzed the incidence and risk factors involved in ventilation-acquired pneumonia in a COVID-19 cohort in three French public hospitals from March to November 2020. Data collected from 161 mechanically-ventilated patients offer a detailed description of critical COVID-19 patients during the first and second wave. After adjusting for confounding factors, risk factors associated with ventilation-acquired pneumonia were dexamethasone, age, sex and the ROX score whereas pre-ICU antibiotic treatment was a protective factor. Dexamethasone has been the only evidence-based therapy having shown a decrease in mortality in severe cases of COVID-19, therefore future robust multicentric studies are needed before questioning the use of this treatment in COVID-19.

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## SERMENT D'HIPPOCRATE

Au moment d'être admis(e) 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(e) dans l'intimité des personnes, je tairai les secrets qui me seront confiés. Reçu(e) 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(e) et méprisé(e) si j'y manque.



## **RESUME**

### **Objectif**

Description des caractéristiques des pneumopathies acquises sous ventilation mécanique et mise en évidence des facteurs de risques associés, chez des patients atteints du COVID-19 hospitalisés en réanimation durant la première année de la pandémie de SARS-CoV-2.

### **Matériels et méthodes**

De Mars à Novembre 2020, inclusion de 161 patients COVID-19 ayant nécessité une ventilation mécanique, hospitalisés en réanimation. Description des caractéristiques des patients atteints de PAVM puis comparaison à un groupe indemne de PAVM afin de rechercher des facteurs de risques éventuels.

### **Résultats**

51% des patients ont présenté une PAVM durant leur hospitalisation en réanimation dont 77% étaient des hommes et 55% présentaient une hypertension artérielle chronique. 38% ont reçu de la dexaméthasone et 47% ont reçu une antibiothérapie avant l'admission en réanimation. 88% des PAVM étaient tardives avec un délai médian d'apparition de 10 jours depuis l'intubation. Les bactéries à gram négatives représentaient 62% des germes et *Pseudomonas spp* était l'espèce la plus représentée. 32% des PAVM étaient liées à des BMR avec comme principale mécanisme de résistance une céphalosporinase hyper-produite.

Les analyses multivariées ont révélé que la dexaméthasone, l'âge, le sexe et le score ROX étaient des facteurs de risques de PAVM tandis que l'antibiothérapie débutée avant l'admission en réanimation était un facteur protecteur.

### **Conclusion**

La PAVM est une complication de réanimation fréquente au sein des patients COVID-19 ventilés atteignant un patient sur deux. Elle est responsable d'une hausse de morbidité du fait de l'augmentation de la durée de séjour en soins intensifs. L'âge élevé, le sexe masculin et la dexaméthasone sont des facteurs favorisant les PAVM. D'autres études de grandes ampleurs, s'intéressant à la dexaméthasone en particulier, sont nécessaires avant de remettre en cause ce traitement ayant fait preuve d'une baisse de mortalité dans le Sars-Cov-2.