Université de Paris
Ecole doctorale Pierre Louis santé publique ED 393

INSERM équipe 1137 IAME équipe 5

Pneumopathie nosocomiale acquise en réanimation : caractérisation en fonction de l'existence et de la durée de ventilation mécanique

Par Wafa Ibn Saied

Thèse de doctorat de Santé Publique, Spécialité Épidémiologie

Dirigée par Jean-François Timsit

Présentée et soutenue publiquement à Paris le 18 septembre 2019

Rapporteurs : Pr Pierre Emanuel Charle, Université de Bourgogne, Dijon
Pr Bertrand Souweine, Université de Clermont Auvergne, Clermont-Ferrand

Examinateurs: Pr Lila Bouadma, Université Paris Diderot, Paris
Pr Jean Ralph Zahar, Université Paris 13 Villetaneuse, Bobigny et Saint Denis
Pr Michael Darmon, Université Paris Diderot, Paris

Directeur de thèse : Pr Jean-François Timsit, Université Paris Diderot, Paris

Résumé en français

Les infections nosocomiales représentent la première cause de mortalité et le premier poste de prescription d'antibiothérapies. Les pneumopathies nosocomiales représentent la première cause de morbi-mortalité en réanimation. Dans un contexte de ressources antibiotiques limitées et une augmentation de l'incidence des germes résistants, nous avons étudié:

1°) Les facteurs de risque de pneumopathies acquises sous ventilation mécanique (PAVM) en tenant compte de la durée de la ventilation mécanique

2°) La différence entre les pneumopathies associées aux soins en réanimation chez les patients non ventilés et les pneumonies acquises sous ventilation mécanique en terme d'étiologie et de conséquences pronostiques.

3°) L'impact de l'adéquation de l'antibiothérapie initiale et les facteurs de risque d'avoir un traitement inadéquat du fait de la résistance bactérienne dans les PAVM à germes gram négatifs.

Nos résultats montrent que :

- ✓ Les pneumonies acquises en réanimation en dehors de la ventilation mécanique invasive (ICU-HAP) et les PAVM sont dues aux mêmes germes avec un risque de décès plus important chez les ICU-HAP.
- ✓ Les PAVM précoces et tardives sont associées à des facteurs de risques différents pouvant justifier de politiques de préventions différentes.
- ✓ L'antibiothérapie préalable et la colonisation préalable à des bactéries multi résistantes expliquent la survenue de PAVM à Gram négatifs résistants.
- ✓ La durée de ventilation invasive avant la survenue de la pneumopathie n'est pas un facteur de risque indépendant de survenue de PAVM à gram négatifs résistants.
- ✓ Un pourcentage d'infection ou de colonisation à bacille gram négatif (BGN) résistant supérieur à 10% dans le centre est associé à la survenue d'une PAVM à gram négatif résistant, indépendamment des facteurs individuels.
- ✓ Les PAVM à *S. maltophilia* surviennent très tardivement, sont très largement associées à une consommation d'antibiotiques élevée, en particulier les pénèmes. Elles sont plus souvent associées à une antibiothérapie initiale inadéquate.

Notre travail confirme la nécessité d'un effort particulier afin d'optimiser le diagnostic et l'adéquation précoce des antibiothérapies, en particulier pour les pneumonies acquises en dehors de la ventilation mécanique et les PAVM à BGN potentiellement résistants aux antibiotiques.

Mots clés

Réanimation; infection nosocomiale ; pneumopathies ; risque compétitif ; germe résistant

Abstract

Healthcare-associated infections are the leading cause of death and the first prescription of antibiotics. Healthcare-associated pneumonia represents the first cause of morbidity mortality in ICU. In the context of limited antibiotic resources and an increase in the incidence of resistant germs, we studied:

1) Risk factors for ventilator acquired pneumonia (VAP) taking into account the duration of mechanical ventilation (MV).

2) If there is a difference between nonventilated and mechanically ventilated pneumonia in terms of etiology and prognostic?

3) What is the impact of the adequacy of the initial antibiotic treatment, and what are the risk factors for inadequate treatment in gram-negative resistant VAP?

Our results show that:

- ✓ Pneumonia acquired by no ventilated patient in the ICU (ICU-HAP) and VAP are due to the same germs with a higher risk of death in ICU-HAP.
- ✓ Early and late VAP are associated with different risk factors that may need different prevention policies.
- ✓ Previous-antibiotic therapy and prior-colonization with multiresistant bacteria explain the occurrence of resistant Gram Negative VAP.
- ✓ Duration of MV before the onset of pneumonia is no longer an independent risk factor for the occurrence of resistant gram-negative VAP.
- ✓ A percentage of infection or colonization with resistant BGN upper to 10% in the centre is associated with the occurrence of a gram-negative, resistant PAVM, regardless of individual risk factors.
- ✓ *S. maltophilia* VAP occurs belatedly and are very widely associated with high antibiotic consumption, especially penems. They are more often associated with inadequate initial antibiotic therapy.

Our work confirms the need for further research to optimize the diagnosis and early adequacy of antibiotics, in particular in ICU-HAP and VAP caused by potentially antibiotic-resistant BGN.

Keywords

ICU; nosocomial infection; PAVM; ICU-HAP; competitive risk; resistant germ

***« Dans les situations critiques, quand on parle avec un calibre bien en pogne, personne ne conteste plus* .Y'a des statistiques là-dessus »**

Michel Audiard
Mélodie en sous-sol

Tables des matières

Introduction 1

Rationnel et état de l'art 3

I) Pneumopathie acquise sous ventilation mécanique (PAVM) 3

1) Incidence 3

2) Épidémiologie 4

3) Facteurs de risque 5

a. Intrinsèques, ou endogènes, liés au patient, « non modifiables » : 5

b. Extrinsèques, ou exogènes, liés à l'hospitalisation « modifiables »: 5

4) Stratégies diagnostiques 7

a. Une stratégie clinique : 7

b. Une stratégie microbiologique : 8

5) Prévention 10

II) L'enjeu des résistances bactériennes 12

1) Résistance dans le monde 13

2) Résistance bactérienne dans les réanimations Françaises 14

III) Particularités de la pneumopathie du sujet non ventilé en réanimation 15

1) Article 1(publié, revue F1000) 18

Présentation de la base de données et introduction des modèles statistiques utilisés 31

IV) Présentation de la base de données OUTCOMEREA® 31

1) La collecte des données 31

2) Qualité de la base de données 32

3) Description des covariables 33

V) Introduction des modèles statistiques utilisés 34

1) Intérêt du modèle de Fine and Gray: 36

2) Variables dépendantes du temps dans le modèle de Cox 37

Chapitre 1 : Facteurs de risque des pneumopathies acquises sous ventilation mécanique : y a-t-il des différences entre les PAVM précoces et tardives ? 41

1) Résumé 41

2) Article 2 (publié, Plos one) 44

Chapitre 2 : Comparaison des pneumonies acquises sous ventilation mécanique et hors ventilation mécanique en réanimation : facteurs de risque et mortalité attribuable. 60

1) Résumé 60

2) Article 3 (publié, Critical care medecine) 62

3) Article 4 (publié, Critical care medecine) 70

Chapitre 3 : Facteurs de risque de pneumopathies acquises sous ventilation mécanique à germe Gram- négatif résistants, particularités du Stenotrophomonas maltophilia 82

1) Résumé 82

2) Article 5 (soumis, Journal of Infection) 84

3) Article 6 (en cours de soumission) 104

Discussion 129

I) PAVM précoces et tardives : est-il utile de continuer à faire cette distinction ? 129

II) Pneumopathies liées aux soins: nouveau défi diagnostique et thérapeutique 131

III) Optimisation du traitement des PAVM à germes gram négatif : comment prédire le risque d'infection à germes potentiellement résistants 133

IV) Pronostic des pneumopathies liées aux soins 134

Conclusions et Perspectives 136

Références 137

Valorisations scientifiques

Publications

- **Ibn Saied W**, Mourvillier B, Cohen Y, Ruckly S, Reignier J, Marcotte G, Siami S, Bouadma L, Darmon M, de Montmollin E, Argaud L, Kallel H, Garrouste-Orgeas M, Soufir L, Schwebel C, Souweine B, Glodgran-Toledano D, Papazian L, Timsit JF. A comparison of the mortality risk associated with ventilator-acquired bacterial pneumonia and nonventilator icu-acquired bacterial pneumonia. Crit Care Med 2019;47:345-352.
- **Ibn Saied W**, Souweine B, Garrouste-Orgeas M, Ruckly S, Darmon M, Bailly S, Cohen Y, Azoulay E, Schwebel C, Radjou A, Kallel H, Adrie C, Dumenil AS, Argaud L, Marcotte G, Jamali S, Papazian L, Goldgran-Toledano D, Bouadma L, Timsit JF. Respective impact of implementation of prevention strategies, colonization with multiresistant bacteria and antimicrobial use on the risk of early- and late-onset vap: An analysis of the outcomerea network. PLoS One 2017;12.
- Barbier F, Pommier C, **Essaied W**, Garrouste-Orgeas M, Schwebel C, Ruckly S, Dumenil AS, Lemiale V, Mourvillier B, Clec'h C, Darmon M, Laurent V, Marcotte G, Lucet JC, Souweine B, Zahar JR, Timsit JF. Colonization and infection with extended-spectrum beta-lactamase-producing enterobacteriaceae in icu patients: What impact on outcomes and carbapenem exposure? J Antimicrob Chemother 2016;71:1088-1097.
- Heyard R, Timsit JF, **Essaied W**, Held L. Dynamic clinical prediction models for discrete time-to-event data with competing risks-a case study on the outcomerea database. Biom J 2019;61:514-534.
- Weiss E, **Essaied W**, Adrie C, Zahar JR, Timsit JF. Treatment of severe hospital-acquired and ventilator-associated pneumonia: A systematic review of inclusion and judgment criteria used in randomized controlled trials. Crit Care 2017;21:017-1755.
- Weiss E, Zahar JR, Garrouste-Orgeas M, Ruckly S, **Essaied W**, Schwebel C, Timsit JF. De-escalation of pivotal beta-lactam in ventilator-associated pneumonia does not impact outcome and marginally affects mdr acquisition. Intensive Care Med. 2016 Dec;42(12):2098-2100. doi: 10.1007/s00134-016-4448-7. Epub 2016 Jul 18

Communication orales

SRLF 2016: différences entre les facteurs de risque de PAVM précoces et tardives

ESCMID 2018: Mortality associated with VAP and hospital pneumonia acquired in ICU

SRLF 2019: Identifying risk factors for resistant Gram-negative bacilli pneumonia in intensive care units

ESCMID 2019: Identifying risk factors for resistant Gram-negative bacilli pneumonia in intensive care units

Dédicaces

A ma Mère,
Merci pour ton amour inconditionnel, ta patience et ton soutien

A mon Père,
Merci de m'avoir toujours poussée et à aller de l'avant

A mon frère,
Un frère, un ami, un confrère merci d'exister dans ma vie

A mes amis de longue date :
Houda ma sœur de cœur, *Fehmi* le meilleur des co-internes d'antan

Aux amis découverts à Paris :
Asma, Rabab, Ali, Elyes, Aymric, Mathias, Amaury, Kevin, Ulia, Cécile et bien sûr Léa

A toute ma belle-famille :
Merci pour votre soutien et compréhension *pépé* Jean-Louis, *mamie* Claire, Frédo, Carine & les petits loulous

A ceux qui m'ont tant appris et qui m'ont guidé au plan professionnel à Tunis et à Paris :
Dr Besbes, Dr Hantous, Dr Riden, Dr Zidi, Dr Darne, Dr Pointet, Dr Haniez, Prof Khelaf

A mes collègues dans les différents services d'urgences et de réa :
Hôpital Henri-Mondor, CH d'Étampes et hôpital de Tenon, merci pour ces moments de partage

A ces patients qui m'auront profondément marquée et que je n'oublierai jamais

A mes co-thésardes :

Anne, Sarah, Emanuelle on a réussi les filles, on est arrivées au bout

A Olivier,
Pour tous les week-ends entre l'hôpital et la thèse je te dis merci pour ta patience et ton soutien

Remerciements

Je souhaite en premier lieu exprimer ma très grande gratitude au Pr Pierre Emmanuel Charle et au Pr Bertrand Souweine qui ont accepté d'être les rapporteurs de cette thèse

A Pr Lila Bouadma, Pr Jean-Ralph Zahar et Pr Michaël Darmon qui me font l'honneur d'accepter de juger ce travail

A Pr Jean-François Timsit, merci d'avoir accepté d'encadrer ma thèse et m'avoir offert la possibilité de travailler sur un sujet aussi intéressant et de m'avoir encadré avec autant de rigueur

A Stéphane Ruckly pour son aide précieuse depuis toutes ses années d'avoir accompagné mes premiers pas de SAS et l'élaboration des différentes études

A Sébastien Bailly, la force tranquille pour son expertise

A l'ensemble de l'équipe DeSCID d'IAME, pour leur bonne humeur Claire, Mathieu, Dara, Donia, Arthur, Rémi, Liem et bien sûr notre Houda

Liste des abréviations

PAVM Pneumopathie acquise sous ventilation mécanique

VM Ventilation mécanique

USI Unité de soin intensif

ICU-HAP Pneumopathie acquise chez les patients non ventilés en réanimation

BGN Bacille gram négatif

SDRA Syndrome de détresse respiratoire aiguë

SARM *Staphylocoque* résistant à la Methiiciline

EBLSE *Enterobacterie* productrice de beta lactamase

CPIS Clinical Pulmonary Infection Score

AT Aspirations trachéales

PDP Prélèvement distal protégé

LBA Lavement broncho-alvéolaire

SOFA score Sepsis-related Organ Failure Assessment score

SM *Stenotrophomonas matophilia*

BGN-R Bacilles Gram négatifs résistants

BGN-S Bacilles Gram négatifs sensibles

PK pharmacocinétique

PD pharmacodynamique

Liste des Figures

Figure 1: Facteurs impliqués dans la survenue d'une PAVM 6
Figure 2: les « Bundles » de prévention de PAVM suggérées en Europe (panel du haut) et aux Etats Unis (panel du bas) 12
Figure 3 : pourcentage de résistance pour *E coli* et *P. aeruginosa* (European Centre for Disease Prevention and Control, 2017). 13
Figure 4: Evolution de la résistance bactérienne aux antibiotiques (données Réa-Raisin 2017) 15
Figure 5: Evénements compétitifs chez un patient ventilé en réanimation 35
Figure 6 : Comparaison entre le Subdistribution hazard et le cause-specific hazard (Lau et al.2009) 37
Figure 7:Période de risque des PAVM et ICU-HAP dans notre étude 38

Liste des Tableaux

Table 1: Exemple de codage des PAVM comme variables temps-dépendantes 39

Introduction

La pneumonie acquise en réanimation est définie comme une pneumonie survenant chez un patient admis en unité de soins intensifs (USI) depuis au moins 48 heures, qu'il soit intubé, ventilé mécaniquement ou non [1, 2]. La plupart des études sur les pneumopathies liées aux soins en réanimation sont axées sur les pneumopathies acquises sous ventilation mécanique (PAVM), en raison de leur incidence plus élevée, des moyens diagnostiques mieux codifiés et une morbi-mortalité significative.

Au cours des 10 dernières années, beaucoup de progrès ont été faits dans la compréhension des pneumopathies associées aux soins et des PAVM avec apparition de nouveaux concepts définissant notamment les événements respiratoires associés à la ventilation[3]. De nouvelles recommandations ont vu le jour tenant compte de ces changements épidémiologiques pour établir de nouvelles stratégies thérapeutiques plus adaptées [4, 5]. L'incidence des pneumopathies liées aux soins est utilisée actuellement comme un indicateur pour la qualité des soins dans les USI en Europe et aux Etats-Unis. Ceci explique l'intérêt majeur de comprendre les facteurs de risque et de mettre en place des moyens de prévention.

Bien que les PAVM représentent une large majorité des pneumonies acquises en réanimation, elles ne concernent qu'une faible proportion des malades admis. En effet, une étude multicentrique a montré que, sur plus de 10 000 admissions en USI, seulement 30% des patients étaient ventilés mécaniquement pendant 48h ou plus [6]. Par conséquent, il est très réducteur de centrer la surveillance, le diagnostic et la prévention sur les PAVM. De plus, les patients non ventilés ayant une pneumopathie acquise en réanimation (ICU-HAP) justifie la ventilation mécanique dans plus d'un tiers des cas dans les rares études sur le sujet et leur impact pronostique est mal connu [7].

Lors de la prise en charge des pneumopathies associées aux soins en réanimation des questions peuvent se poser lors de la prise en charge :

1. Le temps de survenue de la PAVM lors de la VM est-il toujours un déterminant de la résistance ? Que sait-on sur l'écologie des PAVM précoce et tardive ?
2. Les PAVM ont-elles les mêmes facteurs de risque ? Dans quelle mesure la colonisation peut-elle être un facteur de risque de PAVM ? comment peut-on prévenir les PAVM ?
3. Que savons-nous des pneumopathies nosocomiales chez les patients non ventilés mécaniquement en réanimation ? Sont-elles dues aux mêmes micro-organismes ? ont-elles le même pronostic ?
4. Comment peut-on identifier au mieux les patients avec des facteurs de risque de PAVM à germes résistants pour mieux les traiter ?

Pour répondre à ces questions, nous avons articulé notre travail de thèse en **3 chapitres** :

Dans un premier chapitre, nous nous sommes intéressés aux facteurs de risque de pneumopathie en tenant compte de la durée de VM avant la survenue de la PAVM. Nous avons comparé les facteurs de risques de PAVM précoce (seuil de cinq jours de VM) aux PAVM tardives.

Le deuxième chapitre est consacré aux différences épidémiologiques et aux déterminants de pronostic qui existent entre les PAVM et les pneumonies acquises en réanimation en dehors de la ventilation mécanique invasive (ICU-HAP). Nous avons considéré dans l'analyse que certains patients pouvaient présenter plusieurs épisodes de pneumonies nosocomiales consécutives.

Enfin, nous avons étudié les facteurs de risque de développer les PAVM à bactéries à gram négatif potentiellement résistantes aux antibiotiques (*P. aeruginosa*, autres BGN non fermentant, et entérobactéries résistantes aux céphalosporines de 3^{éme} génération) ou naturellement résistantes aux antibiotiques comme *S maltophilia*.

I) Pneumopathie acquise sous ventilation mécanique (PAVM)

L'évaluation des taux de PAVM est un indice de qualité des soins largement utilisé pour comparer les hôpitaux aux États-Unis. Des travaux récents ont mis en évidence que, selon la définition appliquée, le taux de PAVM pouvaient varier de manière très importante.

1) Incidence

Les pneumonies acquises sous ventilation mécanique (PAVM) représentent 30 à 50 % des infections acquises en réanimation et 80% des pneumopathies nosocomiales avec une grande variabilité selon le pays et le type de l'unité de soin intensif (USI) [4, 5, 8, 9]. Devant l'absence de critères de diagnostic standardisé, il est difficile de définir une incidence précise des PAVM. Dans une enquête faite un jour donné sur 13 796 patients admis dans 1 265 USI, 51% des patients avaient une infection nosocomiale, dont 64% soit 4 503 patients avaient une pneumopathie nosocomiale [10] .

De nombreux articles provenant essentiellement des Etats-Unis montrent que l'incidence des PAVM est en nette régression. Sur une période de 2006-2012, Wang et al. montre une baisse de l'incidence des PAVM de 3,1 cas pour 1000 d'hospitalisations à 0,9 cas pour 1000 hospitalisations (une baisse de 71%) dans les USI à recrutement médical contre 5,2 cas à 2 1 cas pour 1000 hospitalisations (une baisse de 62%) dans les USI ayant plutôt un recrutement de patients chirurgicaux [11]. Ce résultat contraste avec une incidence de l'ordre de 1 à 2.5 cas par 1000 jours de ventilation stable ou en discrète diminution dans les pays européens [12, 13]. La diminution de l'incidence constatée par le NHSN pouvait être le résultat d'un renforcement des mesures de prévention. Cependant, la confirmation de la diminution spectaculaire des taux de PAVM aux USA n'a pu être apportée par l'analyse de la base de données Medicare sur les patients de plus de 65 ans atteints de 4 pathologies traceuses. Il est fort probable que la baisse spectaculaire mise en

évidence sur la base NHSN soit expliquée non seulement par une amélioration de la prévention mais surtout par une sous déclaration des PAVM. En effet, la relative subjectivité de la définition utilisée associée au déremboursement des soins des patients développant une PAVM ont probablement influé sur le nombre d'épisodes rapportés. L'utilisation d'une définition plus précise mais surtout plus homogène des PAVM est donc un impératif [14].

2) Épidémiologie

Les PAVM peuvent être dichotomisées soit selon leur délai de survenue par rapport au début de la ventilation : PAVM précoces / tardives, soit selon l'origine des germes responsables « exogènes » et « endogènes ».

Les PAVM précoces survenant entre le 2ème et le 5ème jour après le début de la VM alors que les PAVM tardives compliquant l'évolution d'un malade ventilé après le 5ème jour. Dans le premier cas, les bactéries pathogènes sur-infectantes sont celles présentes dans la flore oropharyngée. La pneumonie résulte d'inhalation précoce de la flore oropharyngée. L'évolution de ces pneumonies est généralement favorable avec une antibiothérapie à spectre étroit. Les PAVM tardives, par contre, sont souvent plus graves, causées par des entérobactéries, des *Staphylocoques aureus* résistants à la méticilline ou des bactéries à Gram-négatifs non-fermentant comme *P aeruginosa* ou *Acinetobacter baumannii*. Elles résultent d'une modification des flores dominantes liées à une pression de sélection antibiotique et/ou à l'acquisition de bactéries multi résistantes du fait d'une transmission croisée.

Une autre façon de catégoriser les PAVM est d'opposer une contamination exogène et endogène. Dans la contamination exogène, les germes proviennent de l'environnement ou d'autres patients, par l'intermédiaire des mains souillées, de la transmission par voie aérienne ou par gouttelettes ou par du matériel contaminé. Dans la contamination endogène, les bactéries sont sélectionnées dans les microbiotes des patients sous la pression des antibiotiques administrés. La sphère oropharyngée représente le réservoir des bactéries colonisant et infectant

les voies aériennes inférieures de même que la réactivation de certains virus « endogènes » et ceci malgré la présence du ballonnet de la sonde endotrachéale.

Les PAVM sont dues aux *Enterobacteriaceae* (25%), *Pseudomonas aeruginosa* (24%), et *S aureus* (20%) en majorité [15]. La présence d'un état de choc, d'une SDRA, la colonisation préalable à bactéries résistantes aux antibiotiques et l'exposition préalable aux antibiotiques sont les principaux facteurs liés à la découverte de bactéries plus résistantes aux antibiotiques [1, 16] . La durée de séjour hospitalier et la durée d'exposition préalable aux antibiotiques plus que la durée de ventilation mécanique sont les éléments qui semblent expliquer le mieux les PAVM à germes résistants aux antibiotiques [17-21].

3) Facteurs de risque

Les PAVM sont reliées dans la littérature à deux catégories de facteurs de risque :

a. **Intrinsèques, ou endogènes, liés au patient, « non modifiables » :** tels que le sexe masculin, une maladie chronique respiratoire ou une immunodépression, un score APACHEII ≥ 15 à l'admission, des troubles de conscience, une sinusite ou une colonisation préalable.

b. **Extrinsèques, ou exogènes, liés à l'hospitalisation « modifiables »:** tels que l'administration de sédatifs ou de curares pendant au moins 2 jours consécutifs, l'extubation accidentelle, une durée de VM prolongée et un rapport de PAO2/FIO2 ≤ à 130 mmHg, le transport durant l'hospitalisation, la douleur inhibant la toux efficace et en favorisant les atélectasies, la chirurgie des voies aéro-digestive haute et la chirurgie thoracique et abdominale.

Ces différents facteurs de risque sont résumés dans la **Fig1**.

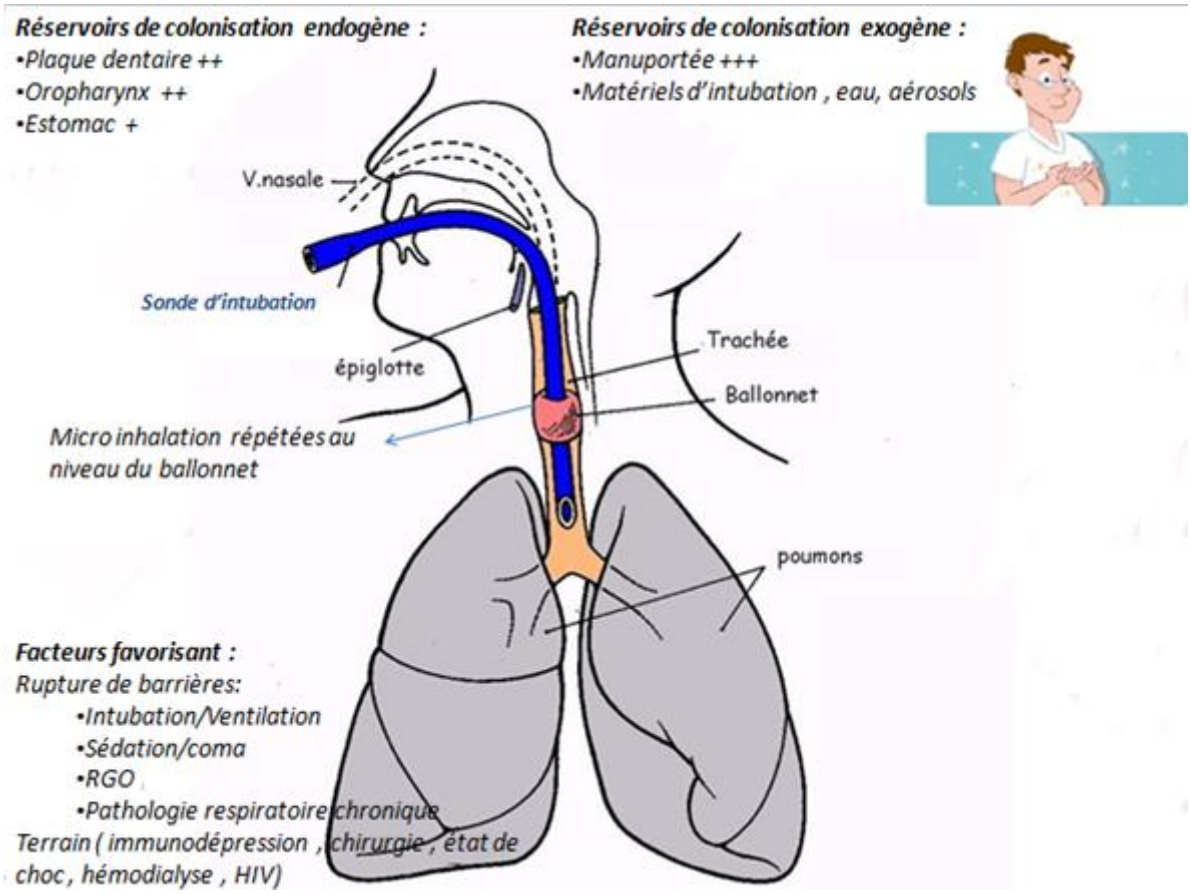


Figure 1:Facteurs impliqués dans la survenue d'une PAVM

On note une certaine évolution dans les facteurs de risque admis dans la littérature[1]. L'âge n'apparait plus comme facteur de risque de survenue de pneumonie. En effet dans une étude européenne multicentrique, la prévalence de la PAVM par 1000 journées de ventilation était de 13.7 entre 45 et 64 ans ; 16.6 pour les patients entre 65 et 74 ans et 13 pour les patients âgés de plus de 75 ans. La régression logistique n'ayant pas permis de démontrer que les âges extrêmes étaient un facteur de risque de PAVM. De même, les patients chirurgicaux ne sont pas plus à risque concernant la survenue de PAVM. L'âge extrême et les patients chirurgicaux sont des éléments de pronostic liés à une mortalité supérieure [22].

L'effet des antibiotiques semble contrasté dans les PAVM. En effet, l'antibiothérapie précoce, c'est-à-dire dans les 8 premiers jours de VM, pourrait avoir un effet protecteur sur la survenue de PAVM précoces, par contre cet effet est discuté pour les PAVM tardives [23, 24]. Vischer et al ont montré que la prise précoce d'antibiotiques lors de la VM réduisait la colonisation par

Haemophilus influenzae, *Staphylococcus aureus* et *Streptococcus pneumoniae*, germes habituellement responsables de PAVM précoces. Cependant, cette prise n'avait pas d'effet sur la colonisation des germes impliqués dans les PAVM tardives comme *Pseudomonas aeruginosa* et *Acinetobacter species* [25]. Le même effet est rapporté pour l'antibioprophylaxie chez les patients ventilés mécaniquement[26]. L'antibiothérapie inadéquate est plus fréquente en cas de PAVM à germes résistants et est associée à une mortalité accrue dans plusieurs études portant sur les PAVM [27-29]. L'incidence croissante de la résistance des germes, pousse les cliniciens à utiliser des antibiotiques à large spectre pérennisant ainsi le cercle vicieux d'augmentation des résistances par sélection de souches plus résistantes.

La prédiction de la résistance bactérienne devant une suspicion de PAVM est difficile. Les éléments clés en sont les antécédents de colonisation à germes résistants, l'antibiothérapie préalable à spectre large. La durée de ventilation mécanique préalable perd de son importance dans les études récentes [1]. Ces éléments sont soulignés dans les derniers consensus Français, Européen et Américain [4, 5, 30]. Une prévalence supérieure à 25% de germe résistant dans l'USI est aussi un facteur de risque d'acquisition de résistance indépendamment du temps de ventilation [18]. Cependant, dans près de 40% des PAVM à bactéries résistantes aucun facteur de risque de résistance n'est retrouvé.

4) Stratégies diagnostiques

Deux stratégies diagnostiques sont utilisées pour le diagnostic de pneumonie nosocomiale:

a. **Une stratégie clinique :** Le diagnostic clinique de pneumonie est évoqué devant l'apparition d'une fièvre associée à des sécrétions trachéales purulentes, une hyperleucocytose ou une leucopénie, l'apparition de nouveaux infiltrats radiologiques et une dégradation des échanges gazeux. Cependant, les signes cliniques et biologiques de pneumonie sont peu spécifiques. De même, les modifications de la radiographie thoracique peuvent résulter d'une pathologie non

infectieuse ou être difficiles à interpréter chez des patients ventilés mécaniquement, notamment en cas de syndrome de détresse respiratoire aiguë (SDRA). Des scores de probabilité ont été établis afin de prédire l'existence une PAVM. On peut citer le CPIS (Clinical Pulmonary Infection Score), combinant 6 variables avec un score CPIS >6 ayant une sensibilité de 93% et une spécificité de 100% dans l'étude princeps non confirmée par les études ultérieures [31].

Les recommandations des consensus américains, européens et français sont en défaveur de l'utilisation de cette définition clinique dans la pratique quotidienne et s'accordent à recommander un prélèvement bactériologique.

b. **Une stratégie microbiologique :** Deux types de prélèvements sont disponibles :

- ***Les prélèvements « non invasifs »*** : Le plus souvent, des expectorations ou aspirations trachéales (AT), dont l'analyse qualitative a une faible spécificité, peuvent induire un diagnostic par excès. Une culture quantitative permet d'obtenir une sensibilité et une spécificité de l'ordre de 80 % pour un seuil de positivité de 10^6 cfu/ml. Cependant, ce résultat peut refléter davantage une colonisation bronchique qu'une infection parenchymateuse. Pour s'affranchir de la colonisation bronchique, un prélèvement distal protégé (PDP) avec ou sans mini LBA à l'aveugle peut été réalisé avec une sensibilité et une spécificité de l'ordre de 80 % pour un seuil de positivité de 10^3 cfu/ml.

- Les prélèvements respiratoires dirigés sous fibroscopie bronchique dits « invasifs » ***:*** prélèvement distal protégé (PDP), brosse télescopique protégée (BTP) ou lavage broncho-alvéolaire (LBA). Les BTP diminuent le risque de contamination

par la flore oropharyngée ; ils ont un seuil de positivité de 10^3 cfu/ml. Les principaux écueils sont une reproductibilité parfois médiocre et un risque de négativité de l'examen si celui-ci est trop dilué, abaissant la concentration des pathogènes isolés. Les limites de faisabilité de la technique sont sa tolérance chez les patients hypoxémiques, pouvant limiter la qualité de l'examen[32]. La culture quantitative du LBA est associée à une sensibilité de l'ordre de 75 % et une spécificité de l'ordre de 85 % pour un seuil de 10^4 cfu/ml [33].

De grandes controverses persistent concernant les échantillons bactériologiques qui devraient être utilisés pour diagnostiquer PAVM. En effet, contrairement aux techniques non invasives, les techniques invasives exigent des cliniciens qualifiés. Les études randomisées qui ont évalué leurs intérêts diagnostiques respectifs ont rapporté des résultats contradictoires [34-36]. Dans une étude comparant le recours aux antibiotiques dans les 2 stratégies diagnostiques ainsi que l'impact sur la mortalité à 14 jours, Fagon et al ont monté la supériorité du diagnostic invasif. En effet, il réduit la mortalité : 16.2% vs 25.8% pour le diagnostic non invasif avec un HR à 1.54. De même, ils ont noté une augmentation du nombre de jours sans antibiotique (5 jours +/-5.1 contre 2.2 jours +/-3.5; $P < 0.001$) ainsi qu'une diminution du SOFA score [35]. Dans une autre étude conduite par *le Canadian Critical Care Trial Group*, les prélèvements invasifs ne semblent pas réduire l'utilisation des antibiotiques, ni impacter la mortalité à vingt-huit jours[34]. Cependant, dans cette étude, le protocole de recherche peut avoir facilité l'arrêt approprié des antibiotiques ou leurs ajustements, minimisant ainsi les différences entre les 2 groupes. Les études de cohorte ont confirmé les avantages potentiels des prélèvements quantitatifs distaux dans la réduction de la durée du traitement et la limitation de la pression de sélection antibiotique sans pour autant augmenter la mortalité ou la durée de séjour en réanimation [37-39]. Dans une étude observationnelle, la mortalité de 89 patients ayant une suspicion clinique de PAVM et un LBA négatif a été comparée en tenant en compte de l'arrêt précoce du traitement antibiotique. Non

seulement l'arrêt précoce des antibiotiques n'est pas associé à une augmentation de la mortalité, mais en plus, il diminue la surinfection avec des germes multi-résistants, comparativement à ceux qui ont gardé l'antibiothérapie 7.5% vs. 35.7%, p = 0.003. Les dernières recommandations américaines et françaises recommandent l'échantillonnage non-invasif avec culture semi-quantitative[4, 30], tandis que les recommandations européennes suggèrent d'obtenir un échantillon distal avec des cultures quantitatives pour la confirmation diagnostique [5]. Malgré cette divergence, les recommandations soulignent l'importance de l'obtention d'un échantillon bactériologique avant de débuter le traitement antibiotique.

5) Prévention

La prévention de la PAVM passe par la limitation du recours à la ventilation invasive, par la limitation de la sédation profonde, et par le sevrage précoce de la ventilation mécanique devenue non nécessaire. A côté de ces facteurs fondamentaux, de nombreuses techniques cherchant à limiter les micros inhalations bactériennes et leur volume ont été testées et sont discutées dans la revue de synthèse. L'utilisation de bouquets de mesures de prévention a permis de réduire l'incidence de la PAVM.

Parmi les facteurs modifiables on peut noter:

- **L'hygiène et la désinfection bucco-pharyngée :** la désinfection à la chlorhexidine de la cavité buccale des patients intubés permettait d'obtenir une réduction de 27 % de l'incidence de PAVM [40].
- **Le contrôle de la pression des ballonnets et les nouvelles sondes endotrachéales :** Le maintien d'une pression constante du ballonnet à des valeurs minimisant les inhalations est capital pour les éviter. L'utilisation du dispositif pneumatique a par exemple permis de diminuer l'incidence des PAVM de 26 % à moins de 10 %[41].
- **L'aspiration sous-glottique** : une méta analyse colligeant les résultats de 13 études randomisées utilisant des systèmes d'aspiration sous-glottique était associée à une

réduction de la durée du séjour à l'unité de soins intensifs (-1,52 jour; p =0,03); diminution de la durée de VM (-1,08 jour ; p = 0,03), et une survenue plus tardive du premier épisode de pneumonie PAVM (2,66 jours; p = 0,001) ainsi qu'à une diminution de 45% des PAVM [42].

L'implémentation de mesures de prévention «*Bundles*» a permis d'additionner les effets bénéfiques des différentes mesures et de diminuer très significativement l'incidence des PAVM. Bouadma et al., ont montré qu'une implantation d'un protocole de soin (avec renforcement de la désinfection hydro-alcoolique des mains, réduction de la prophylaxie de l'ulcère de stress, position semi-assise, maintien de la pression du ballonnet à > 20 cm H_2O, désinfection oropharyngée par une solution de chlorhexidine 4 fois par jour, limitation des aspirations endotrachéales par les infirmières, utilisation préférentielle de sondes oro-gastriques, limitation des changements de circuits du ventilateur, ainsi qu'une protocolisation du sevrage de la ventilation mécanique) permet de diminuer le taux de PAVM[43]. Toutefois ces « *Bundles* » ne sont pas uniformisés avec persistance d'une différence entre les recommandations Européenne et Américaine comme le montre **la Fig. 2.**

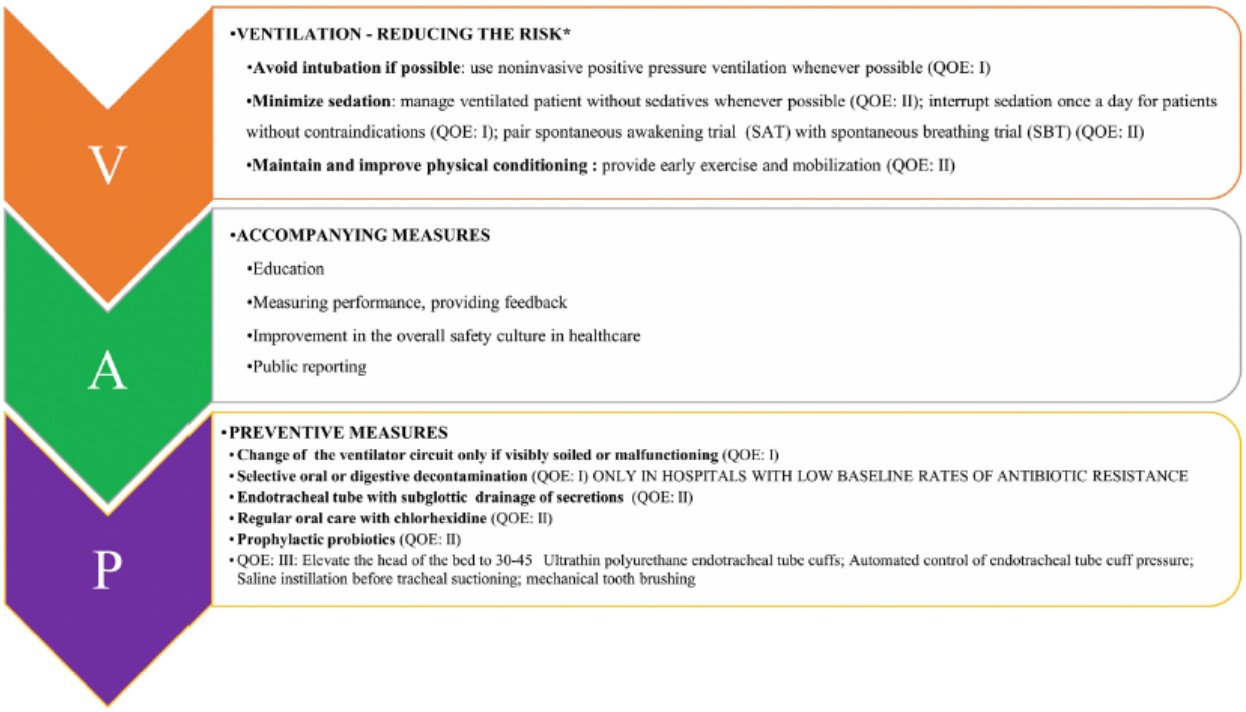


Figure 2: les « Bundles » de prévention de PAVM suggérées en Europe (panel du haut) et aux Etats Unis (panel du bas)

Pour les recommandations Françaises, la prophylaxie anti-ulcéreuse ainsi que l'utilisation de la chlorhexidine n'est pas systématique. A la place c'est l'initialisation précoce de la nutrition entérale ainsi que le contrôle régulier de la pression du ballonnet avec la réalisation d'aspiration sous glottique qui sont préconisés[30].

II) L'enjeu des résistances bactériennes

Il existe deux principaux mécanismes du développement de la résistance bactérienne :

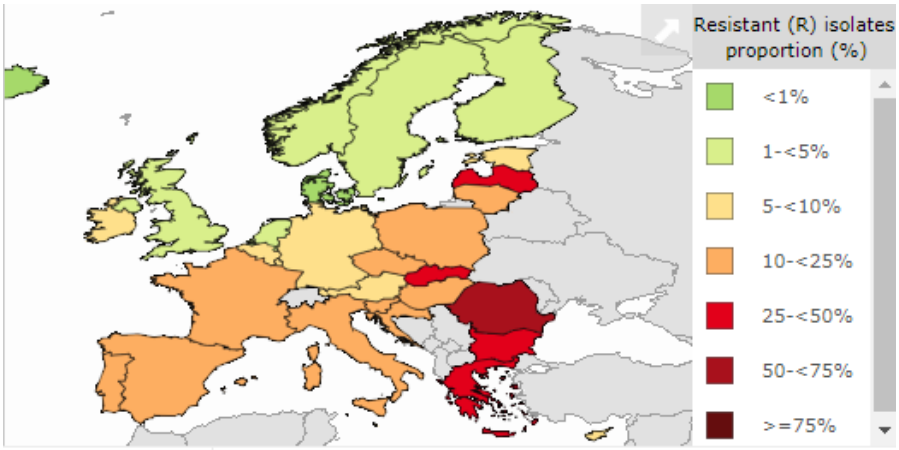
- L'émergence de mutants résistants à partir d'une population sensible en modifiant ou en affectant l'action de l'antibiotique
- L'échange génétique (transformation, la transduction ou la conjugaison)

Quel que soit le mécanisme, la pression de sélection antibiotique joue aussi un rôle essentiel en favorisant la croissance de populations résistantes [44]. L'utilisation raisonnée des antibiotiques est donc, avec la maîtrise de la transmission croisée des bactéries, une nécessité pour contrôler l'augmentation de la résistance et préserver l'activité des antibiotiques.

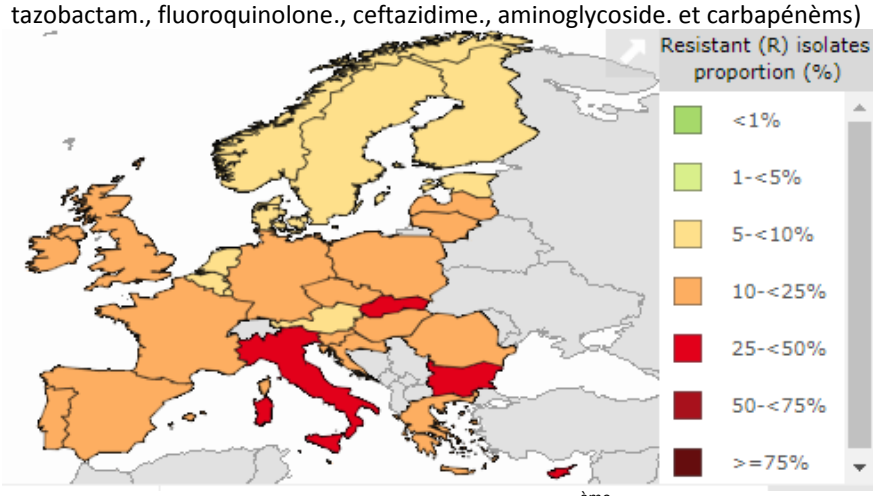
1) Résistance dans le monde

L'augmentation de l'incidence des germes gram-négatifs multi résistants (*Entérobactéries, Pseudomonas aeruginosa, Acinetobacter baumannii*) est un enjeu mondial. Selon l'ECDC le pourcentage de *Pseudomonas aeruginosa* avec une résistance combinée atteint plus de 50% en Europe de l'est, 24% en Italie et avoisine les 30% pour la Grèce. Pour *Acinetobacter baumannii la* résistance combinée aux *carbapoénèmes*, aminoglycosides, fluoroquinolones atteint les 72.6% en Italie ,51% en Espagne et 85% en Grèce.

Cette résistance aux antibiotiques les plus prescrits d'une manière empirique engendre un retard dans l'instauration d'une antibiothérapie adéquate, augmentant ainsi la durée de séjour en réanimation, les coûts liés aux soins ainsi que la mortalité.



Pseudomonas aeruginosa avec résistance combinée (résistant à au moins 3 des antibiotiques listés piperacilline - tazobactam., fluoroquinolone., ceftazidime., aminoglycoside. et carbapénèms)



E. coli résistant aux céphalosporines de 3ème génération

Figure 3 : pourcentage de résistance pour *E coli* et *P. aeruginosa* (European Centre for Disease Prevention and Control, 2017).

2) Résistance bactérienne dans les réanimations Françaises

La coexistence d'un haut niveau de résistance bactérienne et d'un haut niveau de soins favorisant les transmissions croisées fait que les réanimations amplifient potentiellement le risque de diffusion de la résistance bactérienne. Un gros effort de maîtrise de la transmission croisée en France a permis de limiter la diffusion des staphylocoques résistants à la meticilline et des *Acinetobacter baumannii*. Par contre, les données récentes du réseau de surveillance nationale Réa-Raisin montre une augmentation de la prévalence des Entérobactéries résistantes aux céphalosporines de 3ème génération principalement liée aux bêta-lactamases à spectre étendu (BSLE). Cette augmentation est mal comprise, probablement liée à la diffusion communautaire des BLSE. La surconsommation des carbapénèmes qui en résulte fait craindre l'émergence de bactéries résistantes aux carbapénèmes. Cependant, probablement du fait d'un gros effort de dépistage et de prévention de la transmission croisée et de maîtrise de l'utilisation des antibiotiques, la situation reste sous contrôle dans les réanimations françaises. En effet, La résistance du *P.aeruginosa* reste stable sur les 12 dernières années et le nombre de patients porteurs de BGN résistants aux carbapénèmes est stable.

Cependant, l'évolution épidémiologique défavorable observée dans certains pays d'Europe du sud, de l'est, du moyen orient et d'Asie font craindre que cette maîtrise ne soit que temporaire. En effet, non seulement la situation n'a pas pu être maîtrisée en réanimation et à l'hôpital mais la résistance bactérienne a diffusé dans la communauté.

Micro-organisme	Marqueur antibiotique	Pourcentage de résistance dans l'espèce												
		2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
S. aureus	méticilline (SARM)	47,5	39,5	35,6	36,0	34,8	35,0	27,8	25,5	20,4	19,2	16,0	15,2	15,8
	vancomycine	0,5	0,2	0	0,1	0,1	0,3	2,1	2,2	0,4	0,1	0,4	0,5	0,2
E. faecalis	ampicilline	-	-	11,3	17,7	15,3	15,8	12,6	11,3	14,9	6,7	9,5	11,8	7,6
	vancomycine (ERG)	-	-	0,6	1,7	2,9	0,5	2,3	0,0	0,5	0,0	0,6	1,6	0,8
E. faecium	ampicilline	-	-	43,6	52,9	52,6	73,8	68,2	60,0	66,7	57,0	62,8	67,3	76,7
	vancomycine (ERG)	-	-	2,6	5,7	5,1	6,3	5,7	0,0	0,0	3,2	0,6	3,1	1,9
Entérobactéries	C3G	17,2	20,3	20,2	19,9	23,7	27,1	45,4	38,8	35,9	32,9	31,0	28,4	28,3
	BLSE	9,9	6,8	13,2	12,3	13,9	18,4	19,1	17,5	21,4	18,3	17,8	16,8	17,9
	imipénème	-	-	-	-	-	-	2,4	2,4	1,6	1,6	1,0	1,8	1,5
P. aeruginosa	Pipé/tazobactam												28,3	28,0
P. aeruginosa	ceftazidime	22,6	23,3	20,7	22,5	18,2	18,2	28,3	23,6	20,8	17,1	18,7	19,4	21,6
P. aeruginosa	imipénème	-	-	-	-	-	-	22,6	23,4	24,6	19,7	18,4	23,3	19,6
P. aeruginosa	colistine												2,6	2,9
A. baumannii	ceftazidime	78,6	80,2	60,4	58,3	73,6	75,8	54,1	52,3	39,8	47,1	53,5	44,3	40,7
A. baumannii	imipénème	-	-	-	-	-	-	66,9	39,2	38,6	37,5	25,5	29,3	24,0
A. baumannii	colistine												2,1	7,0

Figure 4:Evolution de la résistance bactérienne aux antibiotiques (données Réa-Raisin 2017)

III) Particularités de la pneumopathie du sujet non ventilé en réanimation

Plusieurs différences sont à relever entre la PAVM et les autres pneumonies acquises en réanimation (ICU-HAP). Tout d'abord, on dispose de moins de prélèvements microbiologiques invasifs que dans les PAVM. Pour des raisons évidentes, il est plus simple d'avoir des preuves bactériologiques par la réalisation d'un lavage alvéolaire ou par fibro-aspiration bronchique chez un patient intubé, que chez un patient non intubé. Esperatti et al ont montré que l'agent pathogène était retrouvé chez 42 % des patients ayant une ICU-HAP comparativement à 71 % chez les patients ayant une PAVM. Ce résultat est dû probablement au fait que seulement 84% des ICU-HAP ont une culture de prélèvement microbiologique des voies respiratoires inférieures contre 100% en cas de PAVM [45]. La ICU-HAP est définie comme étant une pneumopathie survenant après 48 heures d'hospitalisation avec des manifestations cliniques et biologiques d'infection, confirmée par un infiltrat radiologique[2]. Cependant un grand nombre de pathologies respiratoires peuvent expliquer cette symptomatologie. En effet d'autres anomalies radiologiques peuvent mimer une ICU-HAP. Le prélèvement microbiologique est fondamental mais risque d'être contaminé par les secrétions oropharyngées et présente un danger chez les patients les plus précaires. L'IDSA/ATS, dans ses dernières recommandations, préconise d'avoir une preuve microbiologique avec un niveau de preuve faible [4]. Une étude mono-centrique a montré que des méthodes invasives sont potentiellement plus dangereuses dans les ICU-HAP [46]. Cependant une

autre étude portant sur les détresses respiratoires des patients d'onco-hematologie montre que la fibroscopie, réalisée en milieu de réanimation sous oxygène à fort débit ou sous ventilation non invasive, n'entrainait pas plus de complications immédiates qu'une stratégie non invasive d'exploration[47]. De plus, en absence de culture des prélèvements des voies respiratoires inférieures et d'un antibiogramme, la désescalade thérapeutique est difficilement envisageable contrairement aux PAVM [48]. De même, la durée du traitement est mieux codifiée pour les PAVM. Faute de prélèvement bactériologique, il y a moins d'essais cliniques conduits chez les patients non ventilés ayant une ICU-HAP, rendant le niveau de preuve des recommandations plus discutable. Cependant, Kollef et al, dans une large étude multicentrique aux USA incluant 835 patients avec une ICU-HAP documentée avec un prélèvement microbiologique mis en culture, ont montré que les ICU-HAP et les PAVM sont causés par les mêmes microorganismes avec une part importante due aux bacilles gram négatifs (BGN) isolés dans 45.8% des ICU-HAP. Les germes responsables des ICU-HAP se répartissaient comme suit : *S. aureus* dans 47.1% des cas, *Pseudomonas spp*. 18.4%, *Klebsiella spp*. 7.1%, *Haemophilus spp.* 5.6%, *E. coli* 4.7%, *Enterobacter spp.* 4.3%, et *Acinetobacter spp.* 2.0% [49]. Ce résultat est confirmé par plusieurs autres études notamment européennes [45, 50-54]. Tout en soulignant l'importance majeure de l'écologie du service d'hospitalisation, la colonisation préalable et la présence ou pas d'un état de choc, les nouvelles recommandations préconisent le même traitement empirique pour les PAVM et les ICU-HAP [4, 5]. Étant donné que les patients en réanimation ont plus de comorbidités avec des critères de gravité et de choc septique, ce choix thérapeutique semble justifié pour les ICU-HAP [4, 5, 52, 55].

Des études récentes ont montré que le nombre de pneumonies nosocomiales en dehors de la ventilation est au moins égal au risque de PAVM. Les ICU-HAP représenteraient environ 20% des pneumonies nosocomiales acquises en réanimation et justifieraient l'intubation des patients dans près d'un quart des cas. Elles sont associées aux mêmes facteurs de risque et engendrant un

allongement de la durée des séjours en réanimation et de la consommation des soins[56, 57]. La mortalité des patients atteints de HAP ne justifiant pas la ventilation mécanique est plus faible que la mortalité des PAVM. A l'inverse, les pneumonies nosocomiales justifiant la ventilation mécanique sont associées à une mortalité plus élevée que les PAVM [7].

La revue de la littérature sur la PAVM a été publiée dans la revue F1000 en décembre 2017 et la discussion sur les pneumonies nosocomiales du sujet non ventilé est reprise dans une revue en cours d'écriture.

1) Article 1(publié, revue F1000)

F1000Research

F1000Research 2017, 6(F1000 Faculty Rev):2061 Last updated: 15 DEC 2017

Check for updates

REVIEW

Update on ventilator-associated pneumonia [version 1; referees: 2 approved]

Jean-Francois Timsit[1,2], Wafa Esaied[1], Mathilde Neuville[2], Lila Bouadma[1,2], Bruno Mourvillier[1,2]

[1]IAME, Inserm U1137, Paris Diderot University, Paris, F75018, France
[2]Medical and Infectious Diseases Intensive Care Unit, AP-HP, Bichat University Hospital, Paris, France

v1 **First published:** 29 Nov 2017, **6**(F1000 Faculty Rev):2061 (doi: 10.12688/f1000research.12222.1)
Latest published: 29 Nov 2017, **6**(F1000 Faculty Rev):2061 (doi: 10.12688/f1000research.12222.1)

Abstract

Ventilator-associated pneumonia (VAP) is the most frequent life-threatening nosocomial infection in intensive care units. The diagnostic is difficult because radiological and clinical signs are inaccurate and could be associated with various respiratory diseases. The concept of infection-related ventilator-associated complication has been proposed as a surrogate of VAP to be used as a benchmark indicator of quality of care. Indeed, bundles of prevention measures are effective in decreasing the VAP rate. In case of VAP suspicion, respiratory secretions must be collected for bacteriological secretions before any new antimicrobials. Quantitative distal bacteriological exams may be preferable for a more reliable diagnosis and therefore a more appropriate use antimicrobials. To improve the prognosis, the treatment should be adequate as soon as possible but should avoid unnecessary broad-spectrum antimicrobials to limit antibiotic selection pressure. For empiric treatments, the selection of antimicrobials should consider the local prevalence of microorganisms along with their associated susceptibility profiles. Critically ill patients require high dosages of antimicrobials and more specifically continuous or prolonged infusions for beta-lactams. After patient stabilization, antimicrobials should be maintained for 7–8 days. The evaluation of VAP treatment based on 28-day mortality is being challenged by regulatory agencies, which are working on alternative surrogate endpoints and on trial design optimization.

Open Peer Review

Referee Status: ✓ ✓

	Invited Referees 1	2
version 1 published 29 Nov 2017	✓	✓

F1000 Faculty Reviews are commissioned from members of the prestigious F1000 Faculty. In order to make these reviews as comprehensive and accessible as possible, peer review takes place before publication; the referees are listed below, but their reports are not formally published.

1 **Saad Nseir**, Lille Univ Hosp, France

2 **Michael Klompas**, Harvard Medical School and Harvard Pilgrim Health Care Institute, USA
Brigham and Women's Hospital, USA

Discuss this article

Comments (0)

Corresponding author: Jean-Francois Timsit (jean-francois.timsit@bch.aphp.fr)

Author roles: Timsit JF: Conceptualization, Supervision, Validation, Writing – Original Draft Preparation, Writing – Review & Editing; **Esaied W**: Resources, Writing – Original Draft Preparation; **Neuville M**: Writing – Original Draft Preparation, Writing – Review & Editing; **Bouadma L**: Writing – Original Draft Preparation, Writing – Review & Editing; **Mourvillier B**: Supervision, Writing – Original Draft Preparation, Writing – Review & Editing

Competing interests: J-FT gave lectures for Merck, Pfizer, and Gilead on antimicrobial therapy and participated in scientific boards of Paratek, Bayer, Merck, and 3M. The other authors declare that they have no competing interests.

How to cite this article: Timsit JF, Esaied W, Neuville M *et al.* **Update on ventilator-associated pneumonia [version 1; referees: 2 approved]** *F1000Research* 2017, **6**(F1000 Faculty Rev):2061 (doi: 10.12688/f1000research.12222.1)

Copyright: © 2017 Timsit JF *et al*. This is an open access article distributed under the terms of the Creative Commons Attribution Licence, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Grant information: The author(s) declared that no grants were involved in supporting this work.

First published: 29 Nov 2017, **6**(F1000 Faculty Rev):2061 (doi: 10.12688/f1000research.12222.1)

Introduction

Hospital-acquired pneumonia (HAP) is defined by an infection of the lung parenchyma that occurred at least 48 hours after hospital admission. Ventilator-associated pneumonia (VAP) develops in intensive care unit (ICU) patients mechanically ventilated for at least 48 hours[1,2]. In contrast, ventilator-associated tracheobronchitis (VAT) is characterized by signs of respiratory infection without new radiographic infiltrates in a patient mechanically ventilated for at least 48 hours[3–5].

In the past 10 years, a great deal of progress has been made in understanding VAP. New concepts of infection-related ventilator-associated complications (IVACs) and ventilator-associated events (VAEs) have been proposed as outcome indicators for prevention strategies[6]. In diagnostic strategies, criteria used to suspect a VAP have been challenged, as have optimal diagnostic tests used to confirm it[7]. Traditional risk factors of VAP due to multidrug-resistant (MDR) bacteria (based on early-onset occurrence and previous antimicrobial therapy) are no longer sufficient. Proposed empirical therapy has been modified accordingly. The optimization of pharmacokinetic/pharmacodynamic parameters is now considered a key factor to ensure adequate and successful therapy. The use of adjunctive aerosolized therapy is also more and more debated. In addition, regulatory agencies are trying to find surrogate endpoints to replace 28-day mortality and to improve the design of randomized clinical trials in this field of investigation[8].

For VAP prevention, the concept of bundle of care was defined. It enabled great successes in VAP prevention; however, the insufficient compliance observed in clinical practice needs to be addressed in order to define easier-to-apply procedures.

This review aims to summarize the available knowledge on VAP, taking profit from the recent publication of North American[7] and European guidelines on VAP management and highlighting recent advances and remaining controversies of the new concepts.

Epidemiology

VAP is the second most common nosocomial infection and the leading cause of death from nosocomial infections in critically ill patients[9]. Its incidence ranges from 5% to 67% depending on case mix and the diagnostic criteria used[10], and the highest rates are in immunocompromised, surgical, and elderly patients. In the US, the incidence of VAP ranges from 2 to 16 episodes per 1,000 ventilator-days[11]. The estimated risk of VAP is 1.5% per day and decreases to less than 0.5% per day after the 14th day of mechanical ventilation[12]. VAP increases the duration of hospitalization by 7 days and health-care costs by approximately $40,000 USD[13].

In published studies, the crude mortality of patients with VAP is highly variable according to case mix and definitions used[14–16]. The definition of attributable VAP mortality is the percentage of deaths that would not have occurred in the absence of the infection. Recent studies have reappraised the impact of VAP on mortality[17–19]. Specifically, given that the risk of VAP is time-dependent, this could potentially result in a significant time-dependent bias because mortality and ICU discharge both act as competing endpoints. Indeed, the most recent studies reported an attributable mortality below 10% with surgical patients[18] whereas those with mid-range illness severity presented the highest associated risk[18,19].

Late-onset VAP is often reported to be associated with higher mortality rates than early-onset VAP[20–22]. Using a multistate model, we confirmed that the attributable mortality for early-onset VAP (5.8%) was considerably lower than for late-onset VAP (10.6%)[18].

Most studies showed that VAP is usually due to aerobic *Enterobacteriaceae* (25%), *Staphylococcus aureus* (20%), *Pseudomonas aeruginosa* (20%), *Haemophilus influenza* (10%), and streptococci[23]. MDR pathogens are more common among late-onset cases. Trouillet *et al.*[24] found that prior use of broad-spectrum antibiotics and mechanical ventilation of more than 7 days were independent risk factors of infection caused by MDR pathogens. However, more recent reports[25–29] have identified similar rates of etiologies in patients with early- versus late-onset VAP. This may be related to the worldwide rise in MDR pathogens; it emphasizes that the local ICU ecology[30] is the most important risk factor for acquiring MDR pathogens, irrespective of the length of intubation. In early-onset pneumonia, the initial VAP severity—that is, the presence of sepsis or septic shock (odds ratio [OR] = 3.7)—and pneumonia that developed in a center with a prevalence of resistant pathogens greater than 25% were independently associated with the presence of resistant pathogens (OR = 11.3)[26].

Risk factors of ventilator-associated pneumonia

VAP results from the microbial invasion of the normally sterile lower respiratory tract, which subsequently can overwhelm the host's defense and establish infection. The major route for microbial invasion is microaspiration of oropharyngeal secretions contaminated by endogenous flora around the endotracheal tube cuff[31]. VAP may also occur by other means[2,32]. In terms of potential reservoirs, it has been suggested that the stomach hosts bacteria that colonize the oropharynx. It has been postulated by some researchers that embolization into the alveoli during suctioning or bronchoscopy is caused by the colonization of the endotracheal tube with bacteria encased in a biofilm[33]. Inhalation of pathogens from contaminated aerosols and direct inoculation are less common, and hematogenous spread from either infected intravascular catheters or bacterial translocation of the gastrointestinal tract lumen are rarer in occurrence.

Consequently, two groups of risk factors for VAP have been identified—namely ventilation-related factors (instrumentation of the airway with an endotracheal tube and subsequent microaspirations) and, less frequently, patient-related factors (for example, pre-existing pulmonary disease)—and only the former is accessible to prevention (Table 1). As a result, VAP, unlike many other nosocomial infections, is difficult to prevent[34].

Prevention

First of all, reducing the exposure to risk factors for VAP is the most efficient way to prevent VAP onset (Figure 1). Therefore, intubation should be avoided whenever possible, and strategies

Table 1. Risk factors of ventilator-associated pneumonia.

Host-related risk factors	Intervention-related risk factors
Medical history and underlying illness	Peri-operative transfusion of blood products
Male gender	Duration of the mechanical ventilation
Extreme age	Reintubation
Prior central nervous system disorder	Supine head position in patients receiving enteral nutrition
Immunocompromised	Antibiotic therapy[a]
Acute underlying diseases	Enteral nutrition
Emergent surgery	Absence of subglottic secretion drainage[b]
Neurosurgery	Intra-hospital transports
Thoracic surgery	Continuous sedation, use of paralytic agents
Cardiac surgery	Nasogastric tubes
Burns	Tracheostomy
Re-intervention	Frequent ventilator circuit changes
Acute severity factors	Intracuff pressure of less than 20 cm H_2O
Organ system failure index of at least 3	
Acute renal failure	
Acute respiratory distress syndrome	
ECMO, intra-aortic support	
Ulcer disease	

Adapted from 2,35–38. [a]Antibiotic therapy protects from early-onset pneumonia due to susceptible bacteria but is a risk factor for late-onset pneumonia due to more resistant organisms. [b]Protective impact of subglottic secretion drainage is mainly demonstrated for cardiac surgery patients. ECMO, extra-corporeal membrane oxygenation.

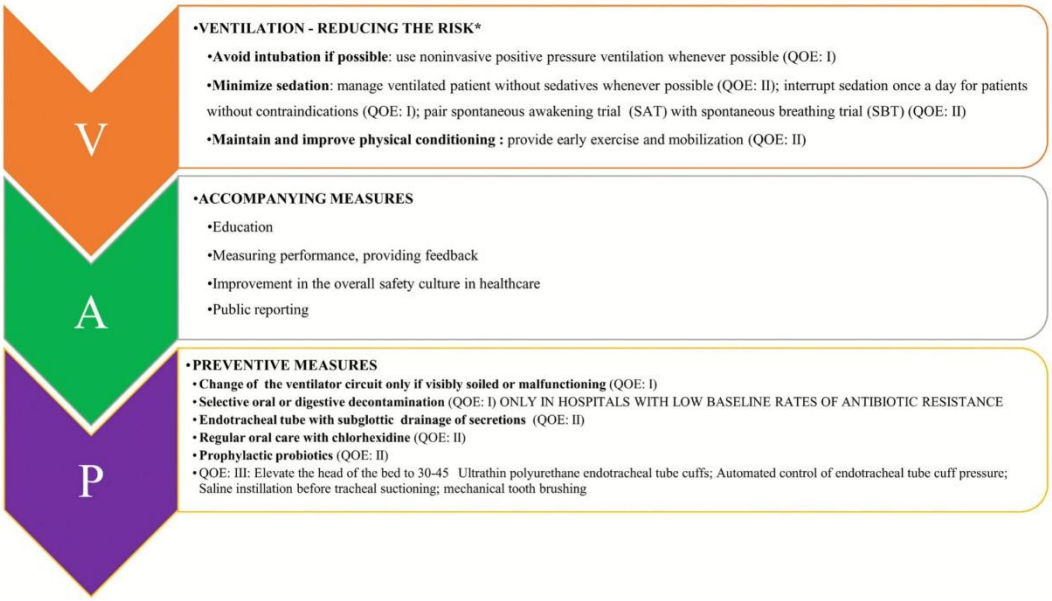


Figure 1. Preventive measures of ventilator-associated pneumonia. Adapted from 37,39. QOE, quality of evidence.

such as non-invasive positive-pressure ventilation, sedation, and weaning protocols should be used to replace or shorten mechanical ventilation. In contrast, recent data suggest that the timing of the tracheotomy does not significantly change VAP incidence[40–43].

Patients at risk of VAP must be managed with a "bundle of preventive measures" (Figure 1). Indeed, no single preventive strategy will efficiently prevent VAP. Bundles group together a small straightforward set of key interventions that are from evidence-based guidelines—generally three to five—and that are expected to result in a better outcome when performed collectively and reliably instead of individually. However, the ideal set of key preventive measures is unknown[44]. Importantly, although studies demonstrated great success in reducing VAP rates using bundle of care in recent years[44–48], meta-analyses showed that most of the preventive measures failed to demonstrate a sustained effect[49]. This conclusion is in line with the absence of substantial improvement of VAP rates in the past decade[50]. Figure 1 lists recommended preventive measures according to their level of evidence.

The sole preventive measures that positively impacted mortality are selective digestive decontamination (SDD) and selective oropharyngeal decontamination (SOD)[51]. Compared with SOD, SDD was associated with a lower mortality, reduced length of stay, lower rates of ICU-acquired bacteremia and candidemia, and lower prevalence of rectal carriage of antibiotic-resistant Gram-negative bacteria but with a pronounced gradual increase in aminoglycoside-resistant Gram-negative bacteria[52]. The main remaining question is the reproducibility of these results out of the Netherlands. Indeed, the antibiotic selection pressure induced by SOD or SDD may outweigh their benefits in countries with high levels of bacterial resistance.

Oral care with chlorhexidine is also debated. An updated meta-analysis focusing on double-blind studies in non-cardiac surgery patients showed that it had no impact on VAP rates or duration of mechanical ventilation or duration of ICU stay[53].

Ecological Effects of Decolonization Strategies in Intensive Care (RGNOSIS), a cluster-randomized study (ClinicalTrials.gov identifier NCT02208154) conducted in six European countries, is currently enrolling 10,800 patients into four arms: control, oral care with chlorhexidine, SOD, and SDD. The study's new insights into these ongoing debates are awaited.

Many possible factors may explain why prevention measures did not result in reductions in mortality, duration of stay, or antibiotic consumption. First of all, the VAP definition may not be sufficiently accurate, especially when tested intervention could not be blinded. Second, in recent studies using modern statistics, the attributable mortality of VAP is only 3–4%, considerably smaller than previously reported[19]. Both factors may induce a dramatic decrease of the power of the studies available.

Even if there is convincing evidence that specific interventions might prevent VAP, translating research into practice remains a challenge (Figure 1). Two European surveys found that 37.0% of ICU physicians[54] and 22.3% of nurses[55] did not comply with the published recommendations for VAP prevention. Beyond the theoretical frame, a great deal of attention must be given to the factors that might facilitate a bundle implementation and allow a sustained compliance. An educational session alone, without an associated behavioral strategy, is unlikely to induce profound behavioral changes. It should be kept in mind that, to engage an individual in a particular behavior and improve compliance, we need to act on predisposing factors (knowledge, perceptions, and beliefs) to favor the access to new processes or technologies and to continually reinforce the behavior by feedback[56,57].

Diagnosis

VAP, VAE, IVAC, and VAT: what do these abbreviations mean?

The diagnosis of VAP is traditionally based on clinical symptoms and radiographic criteria that require further bacteriological confirmation. However, it has been demonstrated that these criteria are inaccurate[14,58,59]. Of note, VAP is now considered an indicator of performance in the US and some other countries. The National Healthcare Society Network reported a considerable decrease in the VAP incidence rate attributed to a multifaceted infection control program and its effective implementation[60]. A 70% decrease of the incidence between 2006 and 2012 was reported by the Centers for Disease Control and Prevention (CDC). But in the same period, the Medicare Patient Safety Monitoring System reported an adjusted average annual change of 0% (95% confidence interval (CI) −0.05 to 0.07) in patients 65 years old or older[60]. These findings emphasize a true discrepancy between rates reported in a quality monitoring program and rates observed in patients' care program.

The discrepancies between results prompted the CDC to promote new objectives of the surveillance based on VAEs. Another important motivation of the CDC was to expand the purview of quality and safety surveillance to encompass multiple complications in mechanically ventilated patients instead of just pneumonia alone.

The VAE surveillance definition algorithm uses three new indicators: ventilator-associated complications (VACs), IVACs, and possible and probable VAP[61]. VAC is the first step of VAE surveillance, with the aim of identifying any complication occurring in mechanically ventilated patients, regardless of the origin or mechanism. To meet the definition of VAC, a mechanically ventilated patient must have at least 2 days of stability or improvement of respiratory parameters—such as a stable or decreasing daily minimum positive end-expiratory pressure (PEEP) or fraction of inspired oxygen (FiO_2)—followed by at least 2 days of worsened oxygenation (diagnosed by an increase of the daily minimum PEEP (at least 3 cm H_2O) or FiO_2 (at least 20%)). The concept of IVAC aims to identify the subgroup of VACs that are potentially related to infection. A VAC associated with an abnormal white blood cell count or a modified temperature becomes an IVAC if the initiation of a new antimicrobial agent is maintained for at least 4 days. With evidence of purulent respiratory secretions or positive results of microbiological tests performed on respiratory tract specimens or both, an IVAC becomes a possible VAP. All of these definitions are summarized in Figure 2.

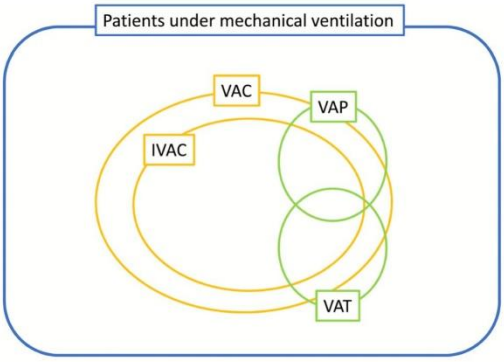


Figure 2. Ventilator-associated events, definitions, and nosology. *Ventilator-associated conditions (VACs)*: at least 2 calendar days of stable or decreasing daily minimum positive end-expiratory pressure (PEEP) or fraction of inspired oxygen (FiO_2) followed by rise in PEEP of at least 3 cm H_2O or rise in FiO_2 of at least 20 points sustained for at least 2 days. *Infection-related ventilator-associated complications (IVACs)*: VAC plus: temperature of less than 36°C or more than 38°C OR white blood cell (WBC) count of not more than 4 or at least 12×10^3 cells/mm^3 AND at least one new antibiotics continued for at least 4 days WITHIN 2 days of VAC onset EXCLUDING first 2 days on the ventilator. *Possible ventilator-associated pneumonia (VAP) (Centers for Disease Control and Prevention [CDC] definitions)*: IVAC plus: criterion 1: Positive culture meeting specific quantitative or semi-quantitative threshold; criterion 2: Purulent respiratory secretions AND identification of organisms NOT meeting the quantitative or semi-quantitative thresholds; criterion 3: Organisms identified from pleural fluid specimen, positive lung histopathology, and positive diagnostic test for Legionella species or selected respiratory viruses WITHIN 2 days of VAC onset EXCLUDING first 2 days on the ventilator. (The updated January 2017 definitions and comprehensive examples are detailed in the CDC National Healthcare Society Network website; https://www.cdc.gov/nhsn/pdfs/pscmanual/10-vae_final.pdf; accessed 23 October 2017.) *VAP*: radiographic criteria (new or progressive and persistent infiltrates or consolidation or cavitation); systemic criteria (temperature of less than 36°C or more than 38°C OR WBC count of not more than 4 or at least 12×10^3 cells/mm^3); pulmonary criteria (at least one of the following: (1) new onset or increase of purulent aspirates and (2) worsening gas exchange). *Ventilator-associated tracheobronchitis (VAT)*: criteria for VAP but without radiographic criteria.

The VAE concept uses objective criteria and their collection can be automated for systematic recording. The VAP definition is still widely discussed, and a recent study showed that applying the various diagnostic criteria to the same patient population resulted in large differences in the incidence of VAP (that is, from 4% to 42%)[62]. Furthermore, even distal quantitative samples are not 100% reproducible[63,64].

This new approach might overcome the inaccuracy of the VAP definition, facilitate its electronic assessment, and make inter-ICU comparisons more relevant. Second, the association between VAE and antibiotic consumption (considering VAC rates and not only IVAC) was a point in favor of using VAC rate as one indicator of ICU quality of care for antimicrobial stewardship programs[12]. Of note, VAE has very low sensitivity and specificity in diagnosing VAP[12]. In our experience, VAP accounted for only 14.5% of the VAC episodes and 27.6% of the IVAC episodes[12]; in addition, not all IVAC episodes were related to a nosocomial infection.

Furthermore, radiological criteria are not taken into account, so that the IVAC definition includes VAT and VAP (Figure 2). Although VAP and VAT are both associated with an increased duration of mechanical ventilation, VAP impact on ICU mortality is higher than that of VAT[27]. Finally, embedding VAP in the larger definition of IVAC may hamper the understanding of VAP pathophysiology and thus its prevention improvement.

Which bacteriological samples should be collected in case of suspicion of ventilator-associated pneumonia?

Great controversies persist about the bacteriological samples that should be used for diagnosing VAP. Of note, when bacteriological analyses are not immediately available, processing of a bacteriological specimen refrigerated after collection is a reliable alternative[65]. Invasive techniques, such as bronchoalveolar lavage or protected specimen brush with quantitative culture, require qualified clinicians. Randomized studies that have evaluated their value as compared with proximal qualitative samples yielded contradictory results[66–68]. In one study with 413 patients[67], the invasive distal quantitative strategy was combined with an algorithm for treatment de-escalation and led to a significant increase in the number of antibiotic-free days at day 14 (5.0 ± 5.1 versus 2.2 ± 3.5) and day 28 (11.5 ± 9.0 versus 7.5 ± 7.6) in comparison with the strategy with non-invasive methods using qualitative cultures. In contrast, the Canadian Critical Care Trial Group reported no impact of distal quantitative samples on the day-28 antibiotic-free days or on survival[66]. However, in that study, the research protocol may have facilitated appropriate discontinuation of antibiotics or targeted therapy in the two groups,

thus minimizing the differences between them. Cohort studies confirmed the potential advantages of distal quantitative samples in narrowing antimicrobial therapy and limiting antibiotic selection pressure without adverse effects on mortality or length of stay[69–71]. Finally, an observational study in 89 patients with clinically suspected VAP and a negative quantitative bronchoalveolar lavage compared patients with early (within one day) and late antibiotic discontinuation. Early discontinuation was associated with a non-significant decrease in mortality and significantly lower risks of overall superinfections (22.5% versus 43%), respiratory superinfections (10% versus 29%), and superinfections due to MDR pathogens (7.5% versus 36%)[72].

Considering available literature, recent US guidelines recommend non-invasive sampling with semi-quantitative culture[7], whereas the European guidelines suggest obtaining distal samples with quantitative cultures to improve the accuracy of results[9]. Despite this discrepancy, the two guidelines agreed that a bacteriological sample should be performed before any antibiotic treatment in order to reduce antibiotic exposure.

Treatment of ventilator-associated pneumonia

The initial treatment of VAP is based on empirical choices; however, an inappropriate initial antibiotic choice is associated with increased mortality[21,73]. In addition, the recovery of MDR bacteria is clearly associated with an increased risk of inappropriate therapy[74]. As discussed earlier, the risk of MDR is conditioned by the local ecological data, previous colonization, and previous antibiotic therapy received by the patients. The increase in the risk of MDR in late-onset infections is challenged by recent studies. Regimens proposed by the North American guidelines are listed in Table 2[7]. An algorithm for an empirical therapy strategy combining guidelines and practical rules is proposed in Figure 3.

Table 2. Empirical treatment of hospital-acquired pneumonia/ventilator-associated pneumonia.

Not at high risk of mortality and no risk factors[a]	Not at high risk of mortality but with factors increasing the likelihood of Gram-negative bacteria	High risk of mortality or receipt of intravenous antibiotics during the prior 90 days
One of the following: Piperacillin-tazobactam 4.5 g IV q6h OR Cefepime 2 g IV q8h Levofloxacin 750 mg IV daily	Piperacillin-tazobactam 4.5 g IV q6h OR Cefepime or ceftazidime 2 g IV q8h OR Levofloxacin 750 mg IV daily Ciprofloxacin 400 mg IV q8h OR Imipenem 1g IV q8h Meropenem 1 g IV q6h	Piperacillin-tazobactam 4.5 g IV q6h OR Cefepime or ceftazidime 2 g IV q8h OR Levofloxacin 750 mg IV daily Ciprofloxacin 400 mg IV q8h OR Imipenem 1g IV q8h Meropenem 1 g IV q6h AND Amikacin 25 (30) mg/kg IV daily OR Gentamicin 5–7 mg/kg IV daily OR Tobramycin 5–7 mg/kg IV daily
	Vancomycin 15 mg/kg IV q8–12h with goal to target 15–20 mg/mL trough level (consider a loading dose of 25–30 mg/kg × 1 for severe illness) OR Linezolid 600 mg IV q12h	Vancomycin 15 mg/kg IV q8–12h with goal to target 15–20 mg/mL trough level (consider a loading dose of 25–30 mg/kg × 1 for severe illness) OR Linezolid 600 mg IV q12h

Adapted from Infectious Diseases Society of America/American Thoracic Society guidelines[7]. [a]Risk factors of multidrug-resistant ventilator-associated pneumonia (VAP) are prior intravenous use within 90 days, septic shock at VAP onset, acute respiratory distress syndrome preceding VAP, five or more days of hospitalization prior to VAP onset, and acute renal replacement therapy prior to VAP onset. IV, intravenous; q, every.

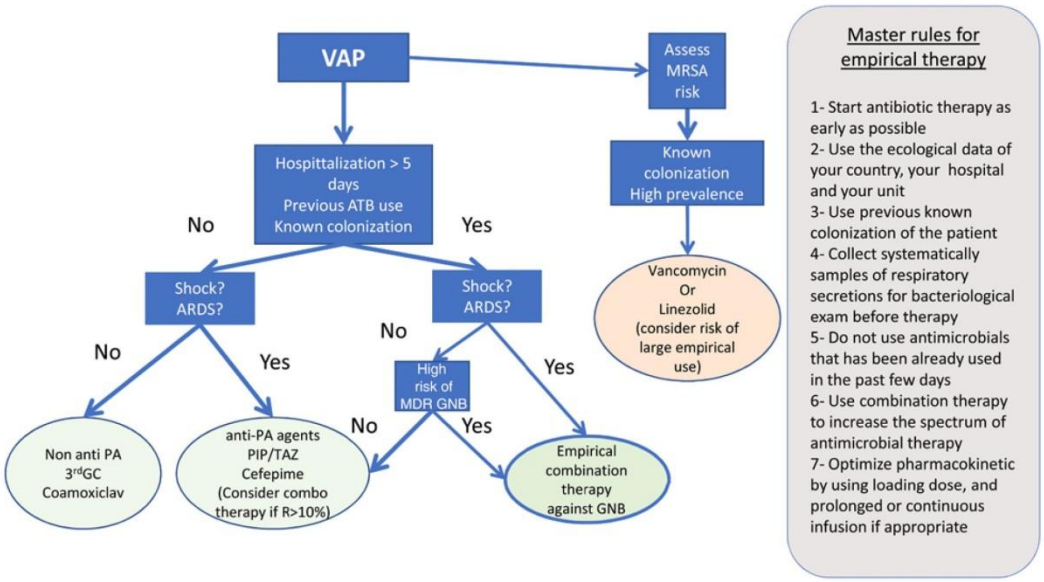


Figure 3. Proposed strategy for empirical therapy. *In areas with a risk of multidrug-resistant and carbapenemase-producing bacteria, the empirical choice should be decided on the basis of local ecology. 3rd GC, third-generation cephalosporin; ARDS, acute respiratory distress syndrome; ATB, antibiotics; GNB, Gram-negative bacteria; MDR, multidrug-resistant; MRSA, methicillin-resistant *Staphylococcus aureus*; PA, *Pseudomonas aeruginosa*; PIP/TAZ, piperacillin-tazobactam; R, Resistant; VAP, ventilator-associated pneumonia.

The challenge for the intensivist is to start an antimicrobial therapy that will be immediately effective while avoiding any overuse of extended-spectrum antimicrobials. New rapid diagnostic tests have been developed but their performances for VAP diagnosis remain to be evaluated[75,76]. Rapid nucleic acid amplification or mass spectrometry-based techniques provide rapid identification of targeted microorganisms. Some of these new tests are also able to detect resistance genes. However, the presence of genes detected by these techniques does not mean that the pathogens are alive or dead, nor does it provide information regarding phenotypic antimicrobial susceptibility. Rapid culture with semi-automated rapid antibiotic susceptibility tests are also in development. Fluorescence *in situ* hybridization-based microscopy identification and antibiotic susceptibility test (ID/AST) systems can evaluate antibiotic susceptibility from respiratory secretions on a previously defined panel of pathogens. A recent pilot study reported promising results: the technique was able to detect pathogens in bronchoalveolar lavage after 5 ± 7 hours of culture and 5 hours of analysis, and sensitivity and specificity were 100% and 97%, respectively[77]. Technical developments with a better selection and quantification of pathogens and resistance patterns are warranted.

Beta-lactams remain a cornerstone antibiotic for the treatment of VAP. Critical care patients exhibit high clearance and distribution volume, which contribute to low blood levels of antimicrobials[78]. Therefore, the doses that should be used to treat the most severe patients are frequently higher than the ones approved by regulatory agencies[79]. For β-lactams, the best results seem to be associated with β-lactam plasma levels up to four times the minimal inhibitory concentration (MIC) of the involved pathogen and during 100% of the interval between each dose[80]. For these agents, a loading dose followed by a continuous infusion may be a relevant method of administration to increase the antibiotic concentration in the blood and the lung lining fluid with a lower risk of neurological[81] or renal[82] toxicity. It is of special importance when bacteria are not fully susceptible or when MICs are high, as for *P. aeruginosa* and MDR Gram-negative bacteria[83].

Combination therapy with aminoglycosides increases the likelihood to immediately achieve an adequate therapy, especially for infection due to MDR Gram-negative bacteria[84]. It is associated with an improved prognosis in the most severe patients[85]. A dose as high as 25 mg/kg of amikacin is required to reach the optimal 60 mg/L peak concentration, even in the case of renal failure. Indeed, the distribution volume of aminoglycosides is not affected by renal dysfunction[86]. However, renal impairment, present in almost 30% of ICU patients, will lead to prolonged intervals between doses, reducing the actual number of peak levels, thus possibly affecting the treatment efficiency.

Indeed, controversies still exist about advantages and disadvantages of aminoglycosides. Ong *et al.* compared empirical therapy of septic shock with or without gentamicin in two Dutch ICUs[87]. One of the ICUs preferentially used aminoglycosides, whereas the other preferentially avoided them. After careful adjustment

on patients' characteristics, they found that gentamicin is an independent predictor of renal failure without affecting mortality. The main limitations of this study include (1) the absence of random allocation, (2) the absence of control on center effect, (3) the setting in two ICUs where the rate of MDR Gram-negative organisms is very low with a minimal risk of inadequate therapy, and (4) the absence of therapeutic drug monitoring for gentamicin. Nevertheless, the study by Ong *et al.*[87] emphasizes the importance of new well-conducted studies comparing antimicrobial therapy with or without aminoglycosides, given with careful therapeutic drug monitoring, for the most severe ICU patients.

Combination therapy with fluoroquinolones was associated with a decrease in the number of days alive without relapse or reinfection in a cohort of patients with VAP due to *P. aeruginosa* or *Enterobacteriaceae* and without any prior treatment with fluoroquinolones[88]. However, the fluoroquinolones are inconstantly active against MDR Gram-negative bacteria and their use is associated with an important risk of emergence of MDR bacteria in the lung and gut microbiota[89].

Concerning extended-spectrum β-lactamase-producing *Enterobacteriaceae* (ESBL-PE), carbapenems remain the first-line agents despite leading to the risk of emergence and spread of carbapenemase-producing *Enterobacteriaceae*[90]. Other options such as piperacillin/tazobactam or a high dose of third-generation cephalosporins administered by continuous infusion could be considered, especially as step-down therapy for ESBL-E with low MICs[30]. New compounds such as ceftolozane/tazobactam and ceftazidime/avibactam have recently been released; however, against HAP/VAP, only the latter was non-inferior to meropenem in a recent randomized trial (REPROVE NCT01808092; results available on ClinicalTrials.gov, not yet published). Temocillin, a ticarcillin derivative that resists ESBL, can be used but only as a step-down therapy for pathogens with MICs below 8 mg/L[91]. For carbapenem-resistant Gram-negative bacteria, colistin is a cornerstone of the treatment, although ceftazidime/avibactam association might be effective. A new association of meropenem and vaborbactam (M-V), recently approved for severe urinary tract infections in the US, has been compared with best available therapy (BAT) in severe infection presumably due to carbapenemase R *Enterobacteriaceae*, including nosocomial pneumonia (TANGO-2 NCT 02168946). The study was presented at the IDWeek convention (in San Diego, CA, in October 2017; abstract 1867) and enrolled 43 patients (more than 80% with *Klebsiella pneumoniae carbapenemase*). It has been stopped prematurely for significant superiority in terms of clinical failure, nephrotoxicity, and non-significant improvement of day-28 mortality of patients with HAP/VAP (M-V 4/16 versus BAT 4/9). Further studies are awaited to confirm these encouraging results and make formal recommendations on its use. An intravenous colistin regimen should be considered with a loading dose of 9 MU and with caution regarding its potential nephrotoxicity[92].

Inhaled antimicrobial therapy may be considered, as this route of administration enables very high concentrations of antimicrobials to be locally delivered[93,94]. However, there are no solutions specifically formulated for inhalation, and a limited number of devices are designed for the nebulization of antibiotics[95,96]. Of note, despite the possible advantages in terms of microbiological eradication and emergence of resistance[97], no impact on patient prognosis has been demonstrated[94,97–99].

In units with rates of methicillin-resistant *Staphylococcus aureus* (MRSA) around 10–20%, include vancomycin or linezolid in the empirical therapy[7]. When the MIC to vancomycin is higher than 1.5 mg/L, the mortality of MRSA pneumonia is higher[100]. Moreover, it is very difficult to reach pharmacokinetic targets using vancomycin[101] without any increase in renal toxicity. Consequently, linezolid should be preferred, particularly in patients with renal impairment or if the MRSA MIC to vancomycin is over 1.5 mg/L[102].

An 8-day antibiotic course appears safe in VAP. This duration can be shortened when a procalcitonin-guided algorithm is used[103] or when ventilator settings (PEEP ≤5 cm H_2O and FiO_2 ≤40%) are stable for 48 hours after antibiotic initiation[104]. As procalcitonin levels above 1.5 ng/mL after three days of treatment seemed strongly associated with a poor outcome[105], re-evaluation of the accuracy of diagnosis and a search for drainable collections (for example, lung abscess or empyema) and revision of therapeutic antimicrobial regimens should be promptly revisited when procalcitonin levels remain high. However, definite data are lacking where *Pseudomonas*, *Acinetobacter*, *Stenotrophomonas*, and MRSA are concerned.

Abbreviations

BAT, best available therapy; CDC, Centers for Disease Control and Prevention; ESBL-PE, extended-spectrum beta-lactamase-producing *Enterobacteriaceae*; FiO_2, fraction of inspired oxygen; HAP, hospital-acquired pneumonia; ICU, intensive care unit; IVAC, infection-related ventilator-associated complication; MDR, multidrug-resistant; MIC, minimal inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; M-V, meropenem and vaborbactam; OR, odds ratio; PEEP, positive end expiratory pressure; SDD, selective digestive decontamination; SOD, selective oropharyngeal decontamination; VAC, ventilator-associated complication; VAE, ventilator-associated event; VAP, ventilator-associated pneumonia; VAT, ventilator-associated tracheobronchitis.

Competing interests

J-FT gave lectures for Merck, Pfizer, and Gilead on antimicrobial therapy and participated in scientific boards of Paratek, Bayer, Merck, and 3M. The other authors declare that they have no competing interests.

Grant information

The author(s) declared that no grants were involved in supporting this work.

Acknowledgments

The authors thank Celine Feger (EMIBiotech) for her editorial assistance.

References

F F1000 recommended

1. American Thoracic Society, Infectious Diseases Society of America: **Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia.** *Am J Respir Crit Care Med.* 2005; **171**(4): 388–416.
PubMed Abstract | Publisher Full Text
2. Chastre J, Fagon JY: **Ventilator-associated pneumonia.** *Am J Respir Crit Care Med.* 2002; **165**(7): 867–903.
PubMed Abstract | Publisher Full Text
3. Craven DE, Hudcova J, Lei Y: **Diagnosis of ventilator-associated respiratory infections (VARI): microbiologic clues for tracheobronchitis (VAT) and pneumonia (VAP).** *Clin Chest Med.* 2011; **32**(3): 547–57.
PubMed Abstract | Publisher Full Text
4. Martin-Loeches I, Papiol E, Almansa R, *et al.*: **Intubated patients developing tracheobronchitis or pneumonia have distinctive complement system gene expression signatures in the pre-infection period: a pilot study.** *Med Intensiva.* 2012; **36**(4): 257–63.
PubMed Abstract | Publisher Full Text
5. Rello J, Riera J, Serrano R: **What's new in ventilator-associated pneumonia?** *Intensive Care Med.* 2015; **41**(11): 1954–6.
PubMed Abstract | Publisher Full Text
6. Magill SS, Klompas M, Balk R, *et al.*: **Developing a new, national approach to surveillance for ventilator-associated events: executive summary.** *Clin Infect Dis.* 2013; **57**(12): 1742–6.
PubMed Abstract | Publisher Full Text | Free Full Text
7. F Kalil AC, Metersky ML, Klompas M, *et al.*: **Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society.** *Clin Infect Dis.* 2016; **63**(5): e61–e111.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation
8. Timsit JF, de Kraker MEA, Sommer H, *et al.*: **Appropriate endpoints for evaluation of new antibiotic therapies for severe infections: a perspective from COMBACTE's STAT-Net.** *Intensive Care Med.* 2017; **43**(7): 1002–1012.
PubMed Abstract | Publisher Full Text | Free Full Text
9. Torres A, Niederman MS, Chastre J, *et al.*: **International ERS/ESICM/ESCMID/ALAT guidelines for the management of hospital-acquired pneumonia and ventilator-associated pneumonia: Guidelines for the management of hospital-acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP) of the European Respiratory Society (ERS), European Society of Intensive Care Medicine (ESICM), European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and Asociación Latinoamericana del Tórax (ALAT).** *Eur Respir J.* 2017; **50**(3): pii: 1700582.
PubMed Abstract | Publisher Full Text
10. Barbier F, Andremont A, Wolff M, *et al.*: **Hospital-acquired pneumonia and ventilator-associated pneumonia: recent advances in epidemiology and management.** *Curr Opin Pulm Med.* 2013; **19**(3): 216–28.
PubMed Abstract | Publisher Full Text
11. Rosenthal VD, Bijie H, Maki DG, *et al.*: **International Nosocomial Infection Control Consortium (INICC) report, data summary of 36 countries, for 2004–2009.** *Am J Infect Control.* 2012; **40**(5): 396–407.
PubMed Abstract | Publisher Full Text
12. Bouadma L, Sonneville R, Garrouste-Orgeas M, *et al.*: **Ventilator-Associated Events: Prevalence, Outcome, and Relationship With Ventilator-Associated Pneumonia.** *Crit Care Med.* 2015; **43**(9): 1798–806.
PubMed Abstract | Publisher Full Text
13. Warren DK, Shukla SJ, Olsen MA, *et al.*: **Outcome and attributable cost of ventilator-associated pneumonia among intensive care unit patients in a suburban medical center.** *Crit Care Med.* 2003; **31**(5): 1312–7.
PubMed Abstract | Publisher Full Text
14. Klompas M: **Does this patient have ventilator-associated pneumonia?** *JAMA.* 2007; **297**(14): 1583–93.
PubMed Abstract | Publisher Full Text
15. Safdar N, Dezfulian C, Collard HR, *et al.*: **Clinical and economic consequences of ventilator-associated pneumonia: a systematic review.** *Crit Care Med.* 2005; **33**(10): 2184–93.
PubMed Abstract | Publisher Full Text
16. Timsit J, Zahar J, Chevret S: **Attributable mortality of ventilator-associated pneumonia.** *Curr Opin Crit Care.* 2011; **17**(5): 464–71.
PubMed Abstract | Publisher Full Text
17. Melsen WG, Rovers MM, Groenwold RHH, *et al.*: **Attributable mortality of ventilator-associated pneumonia: a meta-analysis of individual patient data from randomised prevention studies.** *Lancet Infect Dis.* 2013; **13**(8): 665–71.
PubMed Abstract | Publisher Full Text
18. Nguile-Makao M, Zahar JR, Français A, *et al.*: **Attributable mortality of ventilator-associated pneumonia: respective impact of main characteristics at ICU admission and VAP onset using conditional logistic regression and multi-state models.** *Intensive Care Med.* 2010; **36**(5): 781–9.
PubMed Abstract | Publisher Full Text
19. F Bekaert M, Timsit JF, Vansteelandt S, *et al.*: **Attributable mortality of ventilator-associated pneumonia: a reappraisal using causal analysis.** *Am J Respir Crit Care Med.* 2011; **184**(10): 1133–9.
PubMed Abstract | Publisher Full Text | F1000 Recommendation
20. Ibrahim EH, Ward S, Sherman G, *et al.*: **A comparative analysis of patients with early-onset vs late-onset nosocomial pneumonia in the ICU setting.** *Chest.* 2000; **117**(5): 1434–42.
PubMed Abstract | Publisher Full Text
21. Moine P, Timsit J, De Lassence A, *et al.*: **Mortality associated with late-onset pneumonia in the intensive care unit: results of a multi-center cohort study.** *Intensive Care Med.* 2002; **28**(2): 154–63.
PubMed Abstract | Publisher Full Text
22. Vallés J, Pobo A, García-Esquirol O, *et al.*: **Excess ICU mortality attributable to ventilator-associated pneumonia: the role of early vs late onset.** *Intensive Care Med.* 2007; **33**(8): 1363–8.
PubMed Abstract | Publisher Full Text
23. Park DR: **The microbiology of ventilator-associated pneumonia.** *Respir Care.* 2005; **50**(6): 742–63; discussion 763–5.
PubMed Abstract
24. Trouillet JL, Chastre J, Vuagnat A, *et al.*: **Ventilator-associated pneumonia caused by potentially drug-resistant bacteria.** *Am J Respir Crit Care Med.* 1998; **157**(2): 531–9.
PubMed Abstract | Publisher Full Text
25. Ferrer M, Liapikou A, Valencia M, *et al.*: **Validation of the American Thoracic Society-Infectious Diseases Society of America guidelines for hospital-acquired pneumonia in the intensive care unit.** *Clin Infect Dis.* 2010; **50**(7): 945–52.
PubMed Abstract | Publisher Full Text
26. Martin-Loeches I, Deja M, Koulenti D, *et al.*: **Potentially resistant microorganisms in intubated patients with hospital-acquired pneumonia: the interaction of ecology, shock and risk factors.** *Intensive Care Med.* 2013; **39**(4): 672–81.
PubMed Abstract | Publisher Full Text
27. F Martin-Loeches I, Povoa P, Rodríguez A, *et al.*: **Incidence and prognosis of ventilator-associated tracheobronchitis (TAVeM): a multicentre, prospective, observational study.** *Lancet Respir Med.* 2015; **3**(11): 859–68.
PubMed Abstract | Publisher Full Text | F1000 Recommendation
28. Gastmeier P, Sohr D, Geffers C, *et al.*: **Early- and late-onset pneumonia: is this still a useful classification?** *Antimicrob Agents Chemother.* 2009; **53**(7): 2714–8.
PubMed Abstract | Publisher Full Text | Free Full Text
29. Restrepo MI, Peterson J, Fernandez JF, *et al.*: **Comparison of the bacterial etiology of early-onset and late-onset ventilator-associated pneumonia in subjects enrolled in 2 large clinical studies.** *Respir Care.* 2013; **58**(7): 1220–5.
PubMed Abstract | Publisher Full Text | Free Full Text
30. Timsit JF, Pilmis B, Zahar JR: **How Should We Treat Hospital-Acquired and Ventilator-Associated Pneumonia Caused by Extended-Spectrum β-Lactamase-Producing *Enterobacteriaceae*?** *Semin Respir Crit Care Med.* 2017; **38**(3): 287–300.
PubMed Abstract | Publisher Full Text
31. F Lacherade JC, de Jonghe B, Guezennec P, *et al.*: **Intermittent subglottic secretion drainage and ventilator-associated pneumonia: a multicenter trial.** *Am J Respir Crit Care Med.* 2010; **182**(7): 910–7.
PubMed Abstract | Publisher Full Text | F1000 Recommendation
32. Bouadma L, Wolff M, Lucet JC: **Ventilator-associated pneumonia and its prevention.** *Curr Opin Infect Dis.* 2012; **25**(4): 395–404.
PubMed Abstract | Publisher Full Text
33. Adair CG, Gorman SP, Feron BM, *et al.*: **Implications of endotracheal tube biofilm for ventilator-associated pneumonia.** *Intensive Care Med.* 1999; **25**(10): 1072–6.
PubMed Abstract | Publisher Full Text
34. F Pronovost P, Needham D, Berenholtz S, *et al.*: **An intervention to decrease catheter-related bloodstream infections in the ICU.** *N Engl J Med.* 2006; **355**(26): 2725–32.
PubMed Abstract | Publisher Full Text | F1000 Recommendation
35. Reignier J, Darmon M, Sonneville R, *et al.*: **Impact of early nutrition and feeding route on outcomes of mechanically ventilated patients with shock: a post hoc marginal structural model study.** *Intensive Care Med.* 2015; **41**(5): 875–86.
PubMed Abstract | Publisher Full Text
36. Fitch ZW, Whitman GJ: **Incidence, risk, and prevention of ventilator-associated pneumonia in adult cardiac surgical patients: a systematic review.** *J Card Surg.* 2014; **29**(2): 196–203.
PubMed Abstract | Publisher Full Text
37. F Schwebel C, Clec'h C, Magne S, *et al.*: **Safety of intrahospital transport in ventilated critically ill patients: a multicenter cohort study*.** *Crit Care Med.* 2013; **41**(8): 1919–28.
PubMed Abstract | Publisher Full Text | F1000 Recommendation
38. Bornstain C, Azoulay E, De Lassence A, *et al.*: **Sedation, sucralfate, and antibiotic use are potential means for protection against early-onset ventilator-associated pneumonia.** *Clin Infect Dis.* 2004; **38**(10): 1401–8.
PubMed Abstract | Publisher Full Text
39. Klompas M, Branson R, Eichenwald EC, *et al.*: **Strategies to prevent ventilator-associated pneumonia in acute care hospitals: 2014 update.** *Infect Control Hosp Epidemiol.* 2014; **35 Suppl 2**: S133–54.
PubMed Abstract | Publisher Full Text

40. Huang H, Li Y, Ariani F, *et al.*: **Timing of tracheostomy in critically ill patients: a meta-analysis.** *PLoS One.* 2014; **9**(3): e92981.
PubMed Abstract | Publisher Full Text | Free Full Text

41. F Meng L, Wang C, Li J, *et al.*: **Early vs late tracheostomy in critically ill patients: a systematic review and meta-analysis.** *Clin Respir J.* 2016; **10**(6): 684–92.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

42. F Szakmany T, Russell P, Wilkes AR, *et al.*: **Effect of early tracheostomy on resource utilization and clinical outcomes in critically ill patients: meta-analysis of randomized controlled trials.** *Br J Anaesth.* 2015; **114**(3): 396–405.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

43. Clec'h C, Alberti C, Vincent F, *et al.*: **Tracheostomy does not improve the outcome of patients requiring prolonged mechanical ventilation: a propensity analysis.** *Crit Care Med.* 2007; **35**(1): 132–8.
PubMed Abstract | Publisher Full Text

44. Rello J, Lode H, Cornaglia G, *et al.*: **A European care bundle for prevention of ventilator-associated pneumonia.** *Intensive Care Med.* 2010; **36**(5): 773–80.
PubMed Abstract | Publisher Full Text

45. F Bouadma L, Deslandes E, Lolom I, *et al.*: **Long-term impact of a multifaceted prevention program on ventilator-associated pneumonia in a medical intensive care unit.** *Clin Infect Dis.* 2010; **51**(10): 1115–22.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

46. F Muscedere J, Sinuff T, Heyland DK, *et al.*: **The clinical impact and preventability of ventilator-associated conditions in critically ill patients who are mechanically ventilated.** *Chest.* 2013; **144**(5): 1453–60.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

47. F Morris AC, Hay AW, Swann DG, *et al.*: **Reducing ventilator-associated pneumonia in intensive care: impact of implementing a care bundle.** *Crit Care Med.* 2011; **39**(10): 2218–24.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

48. Speck K, Rawat N, Weiner NC, *et al.*: **A systematic approach for developing a ventilator-associated pneumonia prevention bundle.** *Am J Infect Control.* 2016; **44**(6): 652–6.
PubMed Abstract | Publisher Full Text | Free Full Text

49. F Roquilly A, Marret E, Abraham E, *et al.*: **Pneumonia prevention to decrease mortality in intensive care unit: a systematic review and meta-analysis.** *Clin Infect Dis.* 2015; **60**(1): 64–75.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

50. F Metersky ML, Wang Y, Klompas M, *et al.*: **Trend in Ventilator-Associated Pneumonia Rates Between 2005 and 2013.** *JAMA.* 2016; **316**(22): 2427–9.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

51. F de Smet AM, Kluytmans JA, Cooper BS, *et al.*: **Decontamination of the digestive tract and oropharynx in ICU patients.** *N Engl J Med.* 2009; **360**(1): 20–31.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

52. Oostdijk EAN, Kesecioglu J, Schultz MJ, *et al.*: **Effects of decontamination of the oropharynx and intestinal tract on antibiotic resistance in ICUs: a randomized clinical trial.** *JAMA.* 2014; **312**(14): 1429–37.
PubMed Abstract | Publisher Full Text

53. F Klompas M: **Oropharyngeal Decontamination with Antiseptics to Prevent Ventilator-Associated Pneumonia: Rethinking the Benefits of Chlorhexidine.** *Semin Respir Crit Care Med.* 2017; **38**(3): 381–90.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

54. Rello J, Lorente C, Bodí M, *et al.*: **Why do physicians not follow evidence-based guidelines for preventing ventilator-associated pneumonia?: a survey based on the opinions of an international panel of intensivists.** *Chest.* 2002; **122**(2): 656–61.
PubMed Abstract | Publisher Full Text

55. Ricart M, Lorente C, Diaz E, *et al.*: **Nursing adherence with evidence-based guidelines for preventing ventilator-associated pneumonia.** *Crit Care Med.* 2003; **31**(11): 2693–6.
PubMed Abstract | Publisher Full Text

56. Pittet D: **The Lowbury lecture: behaviour in infection control.** *J Hosp Infect.* 2004; **58**(1): 1–13.
PubMed Abstract | Publisher Full Text

57. Bouadma L, Mourvillier B, Deiler V, *et al.*: **Changes in knowledge, beliefs, and perceptions throughout a multifaceted behavioral program aimed at preventing ventilator-associated pneumonia.** *Intensive Care Med.* 2010; **36**(8): 1341–7.
PubMed Abstract | Publisher Full Text

58. F Nair GB, Niederman MS: **Ventilator-associated pneumonia: present understanding and ongoing debates.** *Intensive Care Med.* 2015; **41**(1): 34–48.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

58. Tejerina E, Esteban A, Fernández-Segoviano P, *et al.*: **Accuracy of clinical definitions of ventilator-associated pneumonia: comparison with autopsy findings.** *J Crit Care.* 2010; **25**(1): 62–8.
PubMed Abstract | Publisher Full Text

60. Dudeck MA, Horan TC, Peterson KD, *et al.*: **National Healthcare Safety Network (NHSN) Report, data summary for 2010, device-associated module.** *Am J Infect Control.* 2011; **39**(10): 798–816.
PubMed Abstract | Publisher Full Text

61. Magill SS, Klompas M, Balk R, *et al.*: **Developing a new, national approach to surveillance for ventilator-associated events*.** *Crit Care Med.* 2013; **41**(11): 2467–75.
PubMed Abstract | Publisher Full Text

62. F Ego A, Preiser JC, Vincent JL: **Impact of diagnostic criteria on the incidence of ventilator-associated pneumonia.** *Chest.* 2015; **147**(2): 347–55.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

63. Timsit JF, Misset B, Francoual S, *et al.*: **Is protected specimen brush a reproducible method to diagnose ICU-acquired pneumonia?** *Chest.* 1993; **104**(1): 104–8.
PubMed Abstract | Publisher Full Text

64. Gerbeaux P, Ledoray V, Boussuges A, *et al.*: **Diagnosis of nosocomial pneumonia in mechanically ventilated patients: repeatability of the bronchoalveolar lavage.** *Am J Respir Crit Care Med.* 1998; **157**(1): 76–80.
PubMed Abstract | Publisher Full Text

65. de Lassence A, Joly-Guillou ML, Salah A, *et al.*: **Accuracy of delayed (24 hours) processing of bronchoalveolar lavage for diagnosing bacterial pneumonia.** *Crit Care Med.* 2004; **32**(3): 680–5.
PubMed Abstract | Publisher Full Text

66. F Canadian Critical Care Trials Group: **A randomized trial of diagnostic techniques for ventilator-associated pneumonia.** *N Engl J Med.* 2006; **355**(25): 2619–30.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

67. Fagon JY, Chastre J, Wolff M, *et al.*: **Invasive and noninvasive strategies for management of suspected ventilator-associated pneumonia. A randomized trial.** *Ann Intern Med.* 2000; **132**(8): 621–30.
PubMed Abstract | Publisher Full Text

68. Solé Violán J, Fernández JA, Benítez AB, *et al.*: **Impact of quantitative invasive diagnostic techniques in the management and outcome of mechanically ventilated patients with suspected pneumonia.** *Crit Care Med.* 2000; **28**(8): 2737–41.
PubMed Abstract | Publisher Full Text

69. Bonten MJ, Bergmans DC, Stobberingh EE, *et al.*: **Implementation of bronchoscopic techniques in the diagnosis of ventilator-associated pneumonia to reduce antibiotic use.** *Am J Respir Crit Care Med.* 1997; **156**(6): 1820–4.
PubMed Abstract | Publisher Full Text

70. Timsit JF, Cheval C, Gachot B, *et al.*: **Usefulness of a strategy based on bronchoscopy with direct examination of bronchoalveolar lavage fluid in the initial antibiotic therapy of suspected ventilator-associated pneumonia.** *Intensive Care Med.* 2001; **27**(4): 640–7.
PubMed Abstract | Publisher Full Text

71. Leone M, Bourgoin A, Cambon S, *et al.*: **Empirical antimicrobial therapy of septic shock patients: adequacy and impact on the outcome.** *Crit Care Med.* 2003; **31**(2): 462–7.
PubMed Abstract | Publisher Full Text

72. Raman K, Nailor MD, Nicolau DP, *et al.*: **Early antibiotic discontinuation in patients with clinically suspected ventilator-associated pneumonia and negative quantitative bronchoscopy cultures.** *Crit Care Med.* 2013; **41**(7): 1656–63.
PubMed Abstract | Publisher Full Text

73. Zahar JR, Timsit JF, Garrouste-Orgeas M, *et al.*: **Outcomes in severe sepsis and patients with septic shock: pathogen species and infection sites are not associated with mortality.** *Crit Care Med.* 2011; **39**(8): 1886–95.
PubMed Abstract | Publisher Full Text

74. Tabah A, Koulenti D, Laupland K, *et al.*: **Characteristics and determinants of outcome of hospital-acquired bloodstream infections in intensive care units: the EUROBACT International Cohort Study.** *Intensive Care Med.* 2012; **38**(12): 1930–45.
PubMed Abstract | Publisher Full Text

75. F Decousser JW, Poirel L, Nordmann P: **Recent advances in biochemical and molecular diagnostics for the rapid detection of antibiotic-resistant *Enterobacteriaceae*: a focus on ß-lactam resistance.** *Expert Rev Mol Diagn.* 2017; **17**(4): 327–50.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

76. Laupland KB, Paiva JA, Timsit JF: **Focus on severe infections.** *Intensive Care Med.* 2017; **43**(7): 1033–6.
PubMed Abstract | Publisher Full Text

77. F Douglas IS, Price CS, Overdier KH, *et al.*: **Rapid automated microscopy for microbiological surveillance of ventilator-associated pneumonia.** *Am J Respir Crit Care Med.* 2015; **191**(5): 566–73.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

78. Roberts JA, Taccone FS, Lipman J: **Understanding PK/PD.** *Intensive Care Med.* 2016; **42**(11): 1797–1800.
PubMed Abstract | Publisher Full Text

79. Weiss E, Essaied W, Adrie C, *et al.*: **Treatment of severe hospital-acquired and ventilator-associated pneumonia: a systematic review of inclusion and judgment criteria used in randomized controlled trials.** *Crit Care.* 2017; **21**(1): 162.
PubMed Abstract | Publisher Full Text | Free Full Text

80. McKinnon PS, Paladino JA, Schentag JJ: **Evaluation of area under the inhibitory**

curve (AUIC) and time above the minimum inhibitory concentration (*T*>MIC) as predictors of outcome for cefepime and ceftazidime in serious bacterial infections. *Int J Antimicrob Agents.* 2008; **31**(4): 345–51.
PubMed Abstract | Publisher Full Text

81. Chow KM, Hui AC, Szeto CC: **Neurotoxicity induced by beta-lactam antibiotics: from bench to bedside.** *Eur J Clin Microbiol Infect Dis.* 2005; **24**(10): 649–53.
PubMed Abstract | Publisher Full Text

82. Roberts JA, Lefrant JY, Lipman J: **What's new in pharmacokinetics of antimicrobials in AKI and RRT?** *Intensive Care Med.* 2017; **43**(6): 904–6.
PubMed Abstract | Publisher Full Text

83. F Abdul-Aziz MH, Sulaiman H, Mat-Nor MB, *et al.*: **Beta-Lactam Infusion in Severe Sepsis (BLISS): a prospective, two-centre, open-labelled randomised controlled trial of continuous versus intermittent beta-lactam infusion in critically ill patients with severe sepsis.** *Intensive Care Med.* 2016; **42**(10): 1535–45.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

84. Martínez JA, Cobos-Trigueros N, Soriano A, *et al.*: **Influence of empiric therapy with a beta-lactam alone or combined with an aminoglycoside on prognosis of bacteremia due to gram-negative microorganisms.** *Antimicrob Agents Chemother.* 2010; **54**(9): 3590–6.
PubMed Abstract | Publisher Full Text | Free Full Text

85. F Kumar A, Zarychanski R, Light B, *et al.*: **Early combination antibiotic therapy yields improved survival compared with monotherapy in septic shock: a propensity-matched analysis.** *Crit Care Med.* 2010; **38**(9): 1773–85.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

86. Boyer A, Gruson D, Bouchet S, *et al.*: **Aminoglycosides in septic shock: an overview, with specific consideration given to their nephrotoxic risk.** *Drug Saf.* 2013; **36**(4): 217–30.
PubMed Abstract | Publisher Full Text

87. F Ong DSY, Frencken JF, Klein Klouwenberg PMC, *et al.*: **Short-Course Adjunctive Gentamicin as Empirical Therapy in Patients With Severe Sepsis and Septic Shock: A Prospective Observational Cohort Study.** *Clin Infect Dis.* 2017; **64**(12): 1731–6.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

88. Planquette B, Timsit JF, Misset BY, *et al.*: ***Pseudomonas aeruginosa* ventilator-associated pneumonia. predictive factors of treatment failure.** *Am J Respir Crit Care Med.* 2013; **188**(1): 69–76.
PubMed Abstract | Publisher Full Text

89. de Lastours V, Chau F, Roy C, *et al.*: **Emergence of quinolone resistance in the microbiota of hospitalized patients treated or not with a fluoroquinolone.** *J Antimicrob Chemother.* 2014; **69**(12): 3393–400.
PubMed Abstract | Publisher Full Text

90. Armand-Lefèvre L, Angebault C, Barbier F, *et al.*: **Emergence of imipenem-resistant gram-negative bacilli in intestinal flora of intensive care patients.** *Antimicrob Agents Chemother.* 2013; **57**(3): 1488–95.
PubMed Abstract | Publisher Full Text | Free Full Text

91. Balakrishnan I, Awad-El-Kariem FM, Aali A, *et al.*: **Temocillin use in England: clinical and microbiological efficacies in infections caused by extended-spectrum and/or derepressed AmpC β-lactamase-producing Enterobacteriaceae.** *J Antimicrob Chemother.* 2011; **66**(11): 2628–31.
PubMed Abstract | Publisher Full Text

92. Vardakas KZ, Rellos K, Triarides NA, *et al.*: **Colistin loading dose: evaluation of the published pharmacokinetic and clinical data.** *Int J Antimicrob Agents.* 2016; **48**(5): 475–84.
PubMed Abstract | Publisher Full Text

93. Niederman MS, Chastre J, Corkery K, *et al.*: **BAY41-6551 achieves bactericidal tracheal aspirate amikacin concentrations in mechanically ventilated patients with Gram-negative pneumonia.** *Intensive Care Med.* 2012; **38**(2): 263–71.
PubMed Abstract | Publisher Full Text

94. F Kollef MH, Ricard JD, Roux D, *et al.*: **A Randomized Trial of the Amikacin Fosfomycin Inhalation System for the Adjunctive Therapy of Gram-Negative Ventilator-Associated Pneumonia: IASIS Trial.** *Chest.* 2017; **151**(6): 1239–46.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

95. Kollef MH: **COUNTERPOINT: Should Inhaled Antibiotic Therapy Be Used Routinely for the Treatment of Bacterial Lower Respiratory Tract Infections in the ICU Setting? No.** *Chest.* 2017; **151**(4): 740–3.
PubMed Abstract | Publisher Full Text

96. F Bassetti M, Luyt CE, Nicolau DP, *et al.*: **Characteristics of an ideal nebulized antibiotic for the treatment of pneumonia in the intubated patient.** *Ann Intensive Care.* 2016; **6**(1): 35.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

97. F Solé-Lleonart C, Rouby JJ, Blot S, *et al.*: **Nebulization of Antiinfective Agents in Invasively Mechanically Ventilated Adults: A Systematic Review and Meta-analysis.** *Anesthesiology.* 2017; **126**(5): 890–908.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

98. F Zampieri FG, Nassar AP Jr, Gusmao-Flores D, *et al.*: **Nebulized antibiotics for ventilator-associated pneumonia: a systematic review and meta-analysis.** *Crit Care.* 2015; **19**(1): 150.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

99. Rattanaumpawan P, Lorsutthitham J, Ungprasert P, *et al.*: **Randomized controlled trial of nebulized colistimethate sodium as adjunctive therapy of ventilator-associated pneumonia caused by Gram-negative bacteria.** *J Antimicrob Chemother.* 2010; **65**(12): 2645–9.
PubMed Abstract | Publisher Full Text

100. F Choi EY, Huh JW, Lim CM, *et al.*: **Relationship between the MIC of vancomycin and clinical outcome in patients with MRSA nosocomial pneumonia.** *Intensive Care Med.* 2011; **37**(4): 639–47.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

101. Patel N, Pai MP, Rodvold KA, *et al.*: **Vancomycin: we can't get there from here.** *Clin Infect Dis.* 2011; **52**(8): 969–74.
PubMed Abstract | Publisher Full Text

102. F Wunderink RG, Niederman MS, Kollef MH, *et al.*: **Linezolid in methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia: a randomized, controlled study.** *Clin Infect Dis.* 2012; **54**(5): 621–9.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

103. F Bouadma L, Luyt CE, Tubach F, *et al.*: **Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial.** *Lancet.* 2010; **375**(9713): 463–74.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

104. F Klompas M, Li L, Menchaca JT, *et al.*: **Ultra-Short-Course Antibiotics for Patients With Suspected Ventilator-Associated Pneumonia but Minimal and Stable Ventilator Settings.** *Clin Infect Dis.* 2017; **64**(7): 870–6.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

105. Luyt CE, Guérin V, Combes A, *et al.*: **Procalcitonin kinetics as a prognostic marker of ventilator-associated pneumonia.** *Am J Respir Crit Care Med.* 2005; **171**(1): 48–53.
PubMed Abstract | Publisher Full Text

Open Peer Review

Current Referee Status: ✔ ✔

Editorial Note on the Review Process

F1000 Faculty Reviews are commissioned from members of the prestigious F1000 Faculty and are edited as a service to readers. In order to make these reviews as comprehensive and accessible as possible, the referees provide input before publication and only the final, revised version is published. The referees who approved the final version are listed with their names and affiliations but without their reports on earlier versions (any comments will already have been addressed in the published version).

The referees who approved this article are:

Version 1

1 **Michael Klompas** [1,2] [1] Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA, USA
[2] Department of Medicine, Brigham and Women's Hospital, Boston, MA, USA
Competing Interests: No competing interests were disclosed.

1 **Saad Nseir** ICU, Lille Univ Hosp, Lille, France
Competing Interests: No competing interests were disclosed.

The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com

F1000Research

IV) Présentation de la base de données OUTCOMEREA®

Pour nos analyses, nous avons utilisé la base de données OUTCOMEREA®mise en place en Décembre 1996. C'est une base de données prospective, alimentée actuellement par 23 services de soins intensifs médicaux et chirurgicaux français. Les bases de données prospectives en réanimation ont un intérêt certain dans la recherche clinique et l'épidémiologie car elles permettent de construire des modèles de prédiction, de prendre en compte l'évolution des paramètres au cours du temps à l'aide de modèles dynamiques et enfin l'acquisition de données à l'inclusion et au cours du séjour du patient permet d'ajuster sur les facteurs de confusion initiaux et dépendants du temps. Ces bases de données permettent aussi d'estimer des liens de causalité via leurs saisies longitudinales à l'aide de méthodes statistiques appropriées. À l'origine de la base Outcomerea®, la saisie des données était manuelle sur des formulaires papier. Une interface graphique de saisie informatique a été développée par la suite pour faciliter et uniformiser la saisie des données. Toutes les applications de cette thèse ont été faites sur la base extraite des archivages de 1997 à février 2016.

1) La collecte des données

Les investigateurs signent une charte d'utilisation de la base de données qui prévoit la saisie complète des données des patients du centre ou la saisie d'un échantillon aléatoire minimal de 50 patients par an. Les données sont recueillies quotidiennement par les médecins seniors avec l'aide d'attachés de recherche clinique formés à cette tâche. La saisie des données a subi deux évolutions : la première interface de saisie, VIGIREA$_{TM}$, a cédé la place en 2000 à RHEA$_{TM,}$ devenue depuis 2017 E-Rhea. Ce logiciel libre de droit d'accès, permet une saisie de haute qualité des données des patients de réanimation. L'outil E-Rhea permet aussi l'édition de compte-rendu

d'hospitalisation, le recueil de la tarification à l'activité, l'élaboration automatique de tableaux de bord au sein des services. Les données sont ensuite archivées avec le logiciel SAS à l'aide d'un programme qui réalise en même temps le contrôle de cohérence des données. Les patients sont suivis jusqu'à leur sortie de réanimation. Durant tout le séjour du patient en réanimation, tous les événements infectieux sont saisis avec précision. On s'intéresse dans notre travail de thèse aux événements infectieux respiratoires : les pneumopathies acquises sous ventilation mécanique (PAVM) et les pneumopathies acquises en réanimation chez les patients non ventilés (ICU-HAP). Pour les pneumonies, il est recommandé d'effectuer des prélèvements invasifs pour les PAVM si possible pour les ICU-HAP ou au moins des prélèvements qualitatifs de bonne qualité avant toute modification de l'antibiothérapie.

Les données de la base OUTCOMEREA® sont actualisées en permanence, elles comptent plus de 19.500 patients pour près de 172.027 jours de suivi lors de l'archivage en février 2016. Un exemple de saisie sur E-Rhea est possible sur ce lien :

2) Qualité de la base de données

Chaque médecin ou attaché de recherche clinique (ARC) impliqué dans la saisie des données suit une formation de 8 heures par un membre du comité de pilotage de base de l'association. L'interface est munie d'alarmes automatiques de saisie et de contrôle. La base anonyme est transmise à l'entrepôt de données où une sauvegarde est immédiatement réalisée, une procédure (sous SAS) permet de tester un grand nombre d'incohérences et de renvoyer des demandes de corrections aux médecins référents dans chaque centre. L'archivage anonyme est assuré par l'équipe INSERM U1137 l'université de Paris (CNIL n° 991279). Un rapport d'erreurs est fait à chaque archivage et aussitôt envoyé aux enquêteurs. Des réanimateurs seniors, experts en réanimation et entraînés au recueil, auditent la saisie. Une école de codage a été créée en 2006 qui permet à la fois la formation initiale et continue des investigateurs et des ARC et organise

annuellement une journée de codage. La formation initiale et continue via l'école de codage, l'uniformisation des définitions ainsi que les alarmes de contrôle de saisie permettent d'avoir une base de données de haute qualité qui peut être utilisée à des fins de recherche épidémiologique.

3) Description des covariables

De nombreuses covariables peuvent avoir un effet sur les événements étudiés : mortalité, facteurs de risque d'avoir un germe résistant. Ces covariables sont soit:

i. **Fixes*, mesurées*** uniquement à l'inclusion : âge, sexe, antécédents médicaux, échelle d'autonomie de Katz, catégorie à l'admission, symptômes à l'admission, diagnostic, SAPSII, existence ou pas d'un sepsis.

ii. **Variables évoluant dans le temps*,*** saisies tous les jours durant le séjour en réanimation : température, prise d'antibiotique, ventilation et paramètres associés, ainsi que le rapport FIO2/PAO2, scores de gravité journalier (SAPSII, SOFA, LOD, TRIO, NEMS), prélèvements bactériologiques effectués, traitement antibiotique administré, remplissage, catécholamines, sédations, transport, colonisation etc.).

Après une revue de la littérature, nous avons sélectionné les variables fixes ou dépendantes du temps, à priori indépendantes entre elles et probablement associées selon le cas à la mortalité attribuable ou pas au risque de survenue de l'événement étudié. Le détail des paramètres intégrés dans les différentes analyses sera donné au début de chaque chapitre.

V) Introduction des modèles statistiques utilisés

Les pneumopathies liées aux soins sont par définition des événements non présents lors de l'admission du patient en USI et qui apparaissent au cours du temps. Cette dimension temporelle est difficile à mettre en évidence par les outils statistiques classiques comme la régression logistique. L'étude des pneumopathies nosocomiales liées aux soins exige une méthodologie rigoureuse pour minimiser le risque de biais et éviter les interprétations trompeuses [58]. De manière générale, l'objectif est d'estimer la probabilité de survenue d'un événement d'intérêt (E1) en considérant l'exposition à une variable (X). Classiquement, la survenue de l'événement d'intérêt est codée de façon binaire :

E1 = 1 si survenue de l'événement

E1 = 0 en l'absence de survenue de l'événement

Lors de son hospitalisation en USI un patient peut passer par plusieurs « états » (infecté, intubé, mort, vivant, …). Les transitions sont les changements d'état possibles. Le modèle statistique doit définir les transitions possibles et impossibles (décès puis infection par exemple, le décès étant un état absorbant). Pour chaque transition, il existe une probabilité de transition et une fonction de risque instantané qui est définie comme la probabilité que la transition d'intérêt ait lieu à l'instant observé sachant qu'elle n'a pas été observée à l'instant précédent. La somme des risques spécifiques de chaque transition est égale au risque global de sortir de l'état précédent à un instant donné. Un événement est dit compétitif lorsqu'il empêche l'observation de l'événement d'intérêt principal (E1). Par exemple, si l'on souhaite étudier la survenue d'une PAVM (E1) chez un patient ventilé mécaniquement, on dit que l'extubation (E2) tout comme le décès en réanimation (E3) sont des événements compétitifs puisqu'ils empêchent d'observer une éventuelle PAVM ***(Fig. 5).***

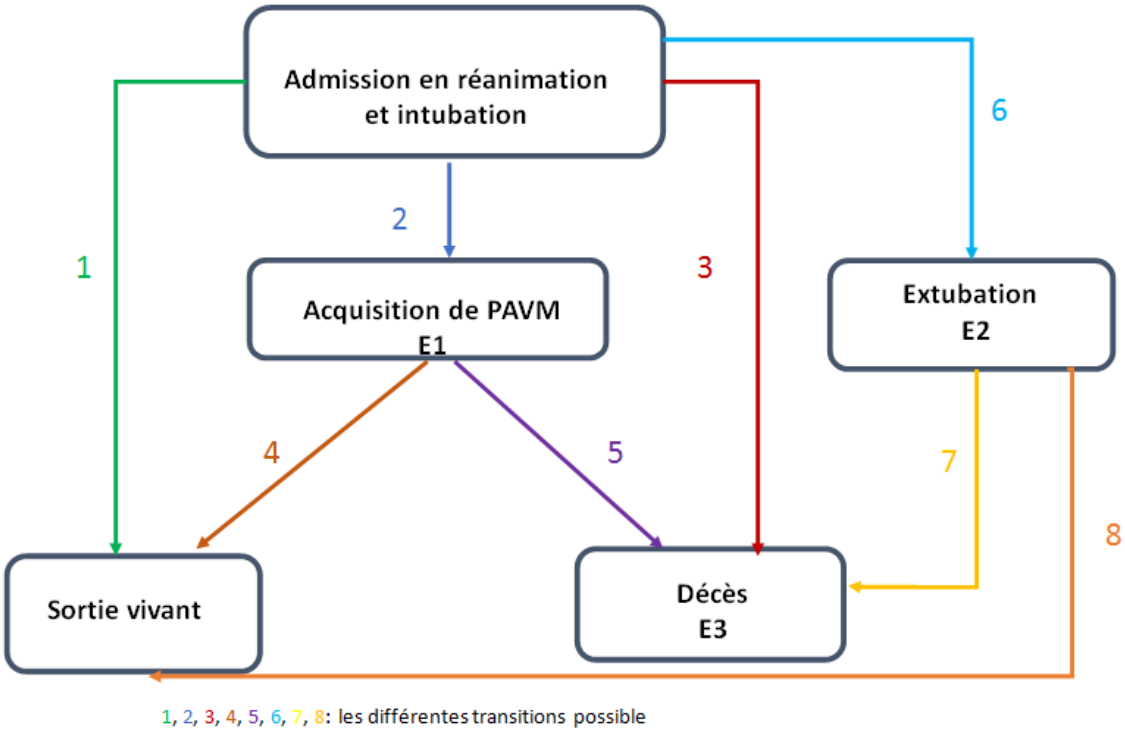


Figure 5:Evénements compétitifs chez un patient ventilé en réanimation

Si on s'intéresse à la survenue de PAVM (E1), l'extubation (E2) ou le décès (E3) sont des évènements en compétition avec notre évènement d'intérêt (E1)

Les modèles de survie classiques ne sont pas adéquats pour l'exploration des pneumopathies liées aux soins. En effet, ce type de modèle présente 2 limites majeures :

- n'empêche pas les biais temps-dépendants

- la censure non informative : les personnes ne présentant pas l'événement d'intérêt au cours de l'étude sont dits « censurées » et sont considérées comme non informatifs. Or, le fait de ne pas voir le décès en fin d'hospitalisation par exemple est tout autant informatif que le fait de ne pas décéder.

D'où l'intérêt d'utiliser les modèles à risque compétitif ou les modèles multi-états dans ce cadre. Il est ainsi possible de mettre en compétition les événements « sorties liées au décès » et « sorties liées à la survie ».

1) Intérêt du modèle de Fine and Gray:

Afin d'étudier le lien entre l'exposition à une variable X (par exemple l'exposition préalable à des antibiotiques) et la survenue d'un événement E1, (par exemple l'acquisition d'une PAVM à germe résistant), on utilise le hazard ratio (HR) qui est le rapport du risque instantané de survenue de l'événement chez les sujets exposés à X : h(t) si (X = 1) et du risque instantané de survenue de l'événement chez les sujets non exposés : h(t) si (X = 0). Pour utiliser le rapport de risque comme estimateur du lien entre l'exposition à X et la survenue de l'événement d'intérêt, il est préférable que sa valeur soit constante au cours du temps, même si les risques instantanés varient; c'est ce que l'on appelle l'hypothèse des risques proportionnels. Il s'agit d'une hypothèse de validité du modèle de Cox. Le modèle de Cox permet d'estimer le lien entre l'exposition à X et le risque de survenue de l'événement d'intérêt E1 si et seulement si la censure est non informative. C'est-à-dire que la survenue de la censure ne modifie pas le risque de survenue de l'évènement. En réanimation, bien entendu, une censure (l'extubation par exemple) modifie le risque de survenue ultérieure de l'évènement (la PAVM par exemple). Il faut donc tenir compte des évènements compétitifs. Afin de prendre en compte tous les risques compétitifs, il est possible d'utiliser le cause-spécifique hazard ratio (cs-HR) qui correspond au HR pour chacun des événements en compétition : chaque événement est tour à tour considéré comme l'événement d'intérêt puis censuré [59]. On obtiendra un modèle de Cox permettant d'estimer le lien spécifique entre la variable X (l'exposition préalable aux antibiotiques) et chacun des événements en compétition E1, E2 et E3. Cependant, cette estimation du risque reste biaisée du fait que les sujets ayant présenté les événements compétitifs (E2, E3) sont également censurés du groupe de sujets à risque de présenter l'événement d'intérêt (E1).

Le modèle de Fine et Gray, qui est une extension du modèle de Cox, permet d'identifier les variables explicatives d'une transition en cas de risque compétitif [60]. Les sujets ayant présenté les événements E2 ou E3 ne sont pas soustraits de la population des sujets susceptibles de

présenter l'événement d'intérêt (***Fig6***)**.** Ils sont ainsi maintenus dans l'échantillon à risque, contrairement au modèle de Cox [61]. Dans ce modèle, la probabilité de l'événement d'intérêt est estimée par la fonction de sous-distribution et l'estimateur est le subdistribution hazard ratio (sHR). L'interprétation est plus aisée que celle des cs-HR. Dans notre situation, un s-HR Hospitalisation->décès supérieur à 1 signifiera un risque augmenté de décès lorsque le patient est exposé à une pneumonie nosocomiale.

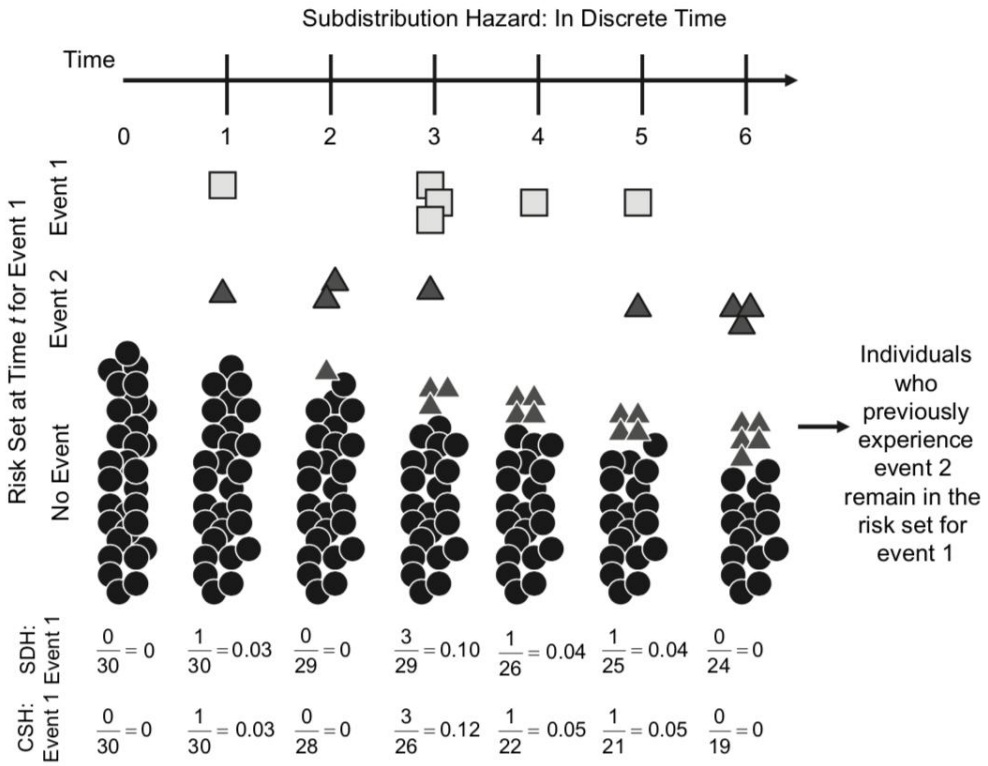


Figure 6 : Comparaison entre le Subdistribution hazard et le cause-specific hazard (Lau et al.2009)

Au début de la période, on a 30 individus à risque (cercles pleins). Au fil du temps, les individus ont soit l'événement 1 (carré plein) ou l'événement 2 (triangle plein). Les patients ayant l'événement en compétition (événement 2 : triangle plein), sont maintenus dans le pool des patients à risque pour l'événement 1 (rond plein). Ainsi, au fil du temps de suivi, une proportion plus grande de triangles compose le pool des patients à risque. Elle correspond aux individus ayant eu l'événement en compétition avant ce moment. Étant donné que les individus sont maintenus dans l'ensemble de risque, le SDH a tendance à être plus bas que le CSH

2) Variables dépendantes du temps dans le modèle de Cox

Lorsque l'on souhaite étudier l'impact de la survenue d'une PAVM sur le décès, le fait de considérer la variable « présence d'une PAVM » comme facteur fixe lors de l'inclusion est une erreur. En effet, d'une part, la date de survenue de la PAVM varie dans le temps pour chaque patient, et d'autre part, il est possible d'observer plusieurs événements PAVM pour un patient lors d'un même séjour en réanimation. Le modèle de Cox permet d'introduire la PAVM comme étant

une variable dépendante du temps [62, 63]. Cela permet alors de prendre en compte la modification de l'exposition d'un sujet à la PAVM au cours de son suivi. Un patient peut par ailleurs avoir une intubation puis être extubé et devenir à risque pour une ICU-HAP **(*Fig* 7)** .Pour tenir compte de la répétition éventuelle de l'exposition à la PAVM (ou aux ICU-HAP), le codage est catégoriel : la survenue d'un nouvel épisode de PAVM en cours de séjour chez un patient ayant déjà eu une PAVM entraîne une modification de la valeur de la variable dépendante du temps PAVM qui passe alors de 0 en cas d'absence de PAVM à 1 en cas d'un épisode, 2 en cas de 2 épisodes et 3 en cas de 3 épisodes **(Table 1).**

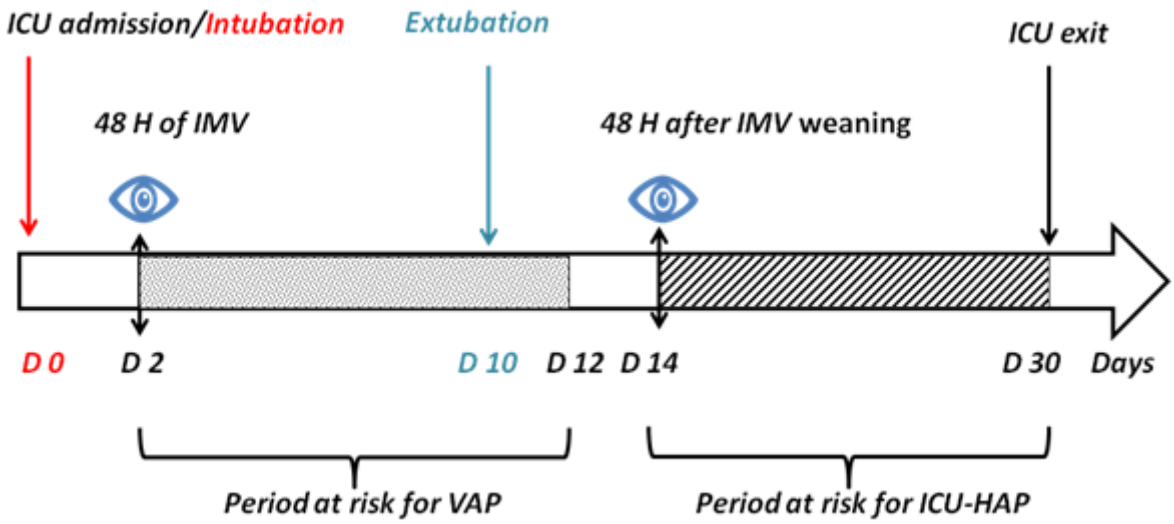


Figure 7:Période de risque des PAVM et ICU-HAP dans notre étude

Le patient hospitalisé en USI intubé depuis plus de 2 jours devient à risque de développer une PAVM. Ensuite, une amélioration clinique permet l'extubation a J 10, mais le patient demeure à risque de PAVM encore 2 jours après l'extubation (jusqu'au jour 12). Le patient devient à risque pour une ICU-HAP à J 14. Nous ne prenons en compte dans notre analyse que la première période à risque pour la PAVM (de J2 à J12) et pour ICU-HAP (de J14 à J30).

Table 1: Exemple de codage des PAVM comme variables temps-dépendantes

NUMHOP	idSejour	VAP1	VAP2	VAP3	duree_VM	date_P1_VAP	date_fin_risque_VAP	vap_delai_cox30	VAP-TD
1000	2	.	.	.	24	29/04/2000	23/05/2000	30	0
1000	3	.	.	.	13	04/05/2000	17/05/2000	30	0
1000	9	7	.	.	18	20/05/2000	07/06/2000	30	1
1000	41	10	.	.	21	30/06/2000	21/07/2000	21	1
1000	248	3	.	.	23	14/06/2001	07/07/2001	30	1
1000	126	2	7	.	21	17/10/2000	07/11/2000	21	2
1000	153	1	26	.	39	13/11/2000	22/12/2000	30	2
1000	161	2	22	.	38	29/11/2000	06/01/2001	30	2
1000	58	3	6	19	45	13/08/2000	27/09/2000	30	3

NUMHOP /idSejour : identifiant centre et séjour
VAP1 : jour de survenue de la 1 ére VAP, T0 correspond au premier jour à risque de faire une VAP (plus de 2 jours de VM)
VAP2 : jour de survenue de la 2 ére VAP, T0 correspond au premier jour à risque de faire une VAP (plus de 2 jours de VM)
VAP3 : jour de survenue de la 3 ére VAP, T0 correspond au premier jour à risque de faire une VAP (plus de 2 jours de VM)
Duree_VM : débute à T0 . Une extubation de 2 jours ou une sortie de réa représente la fin de la période,
Date_P1_VAP : date de début de la première période de risque de VAP
Date_fin_risque_VAP : fin de la période de risque de VAP
Vap_delai_cox30 : délai de suivi du Cox pour la population à risque de faire une VAP. Le T0 correspond au premier jour à risque de faire une VAP. L'événement est le décès, la censure est la date de dernière nouvelle. Une censure globale à 30 jours est appliquée. Les patients sortis pour « domicile » ou « long séjour » sont considérés vivant sans événement à J30
VAP-TD : codage catégoriel selon le nombre d'épisode de PAVM, pour tenir compte de la répétions éventuelle de notre évènement d'intérêt au cours du temps

Si on prend l'exemple du patient avec un numéro d'hospitalisation et identifiant séjour 1000/2, il est ventilé pendant 24 jours sans avoir de PAVM la variable VAP-TD est codée 0. Pour le patient 1000/9 ventilé pendant 18 jours avec survenue d'une VAP à J 7 du début du risque, la variable VAP-TD est codé 1. Le patient 1000/58 ayant 3 VAP lors de sa période à risque respectivement à J3, J6 et J19 VAP-TD est codé à 3.

Dans notre travail de thèse, nous nous sommes intéressés dans un premier temps à l'identification des facteurs de risques de survenue de pneumopathies précoces et tardives en utilisant un model Fine and Gray stratifié sur le centre. Dans un deuxième temps, nous avons procédé à une comparaison des facteurs de risque des pneumonies acquises sous ventilation mécanique et hors ventilation mécanique en réanimation ainsi que la mortalité attribuable en utilisant un modèle de Cox avec une variable sur le temps dépendante (PAVM et ICU-HAP). La troisième partie étant consacrée à la détermination des facteurs d'acquisition de pneumopathie à germes résistants avec une étude cas-témoins pour les facteurs de risque de *Stenophomonas maltophilia* et un modèle mixte linéaire généralisé pour les facteurs de risque de germe gram négatifs potentiellement résistants (BGN non fermentant et entérobactérie).

Chapitre 1 : Facteurs de risque des pneumopathies acquises sous ventilation mécanique : y a-t-il des différences entre les PAVM précoces et tardives ?

1) Résumé

Il est admis, bien que discuté, dans la littérature qu'il y a une différence entre les germes responsables de PAVM précoces et tardives, avec plus de résistance pour les PAVM tardives [1, 64]. Cette différence de pathogènes impliqués serait expliquée en grande partie par une différence dans la physiopathologie. Au cours de l'hospitalisation il y a un changement au niveau des germes colonisant la trachée avec apparition de réservoir gastrique de germes plutôt résistants tels que les BGN et les *Staphylococcus aureus* résistants à la meticilline (SARM). En effet, les PAVM précoces sont dues à la flore endogène avec une inoculation directe lors de l'intubation ou par des micro-inhalations précoces, alors que les PAVM tardives sont dues à une flore modifiée par l'utilisation des antibiotiques et probablement favorisées par l'immunoparalysise post-agressive et les altérations de l'immunité broncho-pulmonaires induite par la ventilation mécanique. Nous avons souhaité caractériser les facteurs de risque de PAVM précoces et tardives pour identifier les facteurs modifiables et leurs impacts potentiels et proposer des attitudes de prévention différentes pour les deux types de PAVM.

Les patients ventilés pour au moins 48 heures de la base OUTCOMEREA étaient éligibles. 7 784 patients étaient à risque d'avoir une PAVM. Les PAVM qui surviennent entre le 3ème et le 6ème jours de VM sont définis comme précoces, celles qui surviennent à partir du 7ème jour étaient considérées comme tardives. Un modèle de sub-distribution de Fine et Gray est utilisé pour tenir compte des événements en compétition avec la PAVM. Les patients étaient censurés après le 28ème jours de VM ou en cas de décès. Un effet « période » est étudié en tenant compte de

l'évolution des pratiques et de l'implantation des «*Bundle*» de prévention des PAVM. Trois périodes de temps sont définies (avant 2001, entre 2001 et 2006 et après 2006). L'incidence de PAVM dans notre étude était de 19%, similaire à celle retrouvée dans la littérature [16, 64]. Sur les 1.234 PAVM observées, 40.2% étaient précoces et 59.8% tardives. Le sexe masculin est le seul facteur de risque en commun augmentant respectivement de 1.33 (1.09-1.63) et de 1.23 (1.06-1.43) le risque de survenue de PAVM précoces et tardives. L'admission avec une comorbidité (une insuffisance rénale ou respiratoire chronique) était reliée à la survenue de PAVM précoces. Une altération de l'état de vigilance, avec un Glasgow effectif entre 8 et 13, augmente de 1.62 le risque de survenue de PAVM précoces. Pour les PAVM tardives, l'admission pour une exacerbation de BPCO, une pneumonie ou une immunodépression augmentaient respectivement le risque de survenue de PAVM tardives de 1.24, 1.26 et de 1.27.

L'effet de la période n'est retrouvé que pour les PAVM précoces avec un effet protecteur après 2006. Ce résultat est souligné déjà par d'autres études, notamment celles de Bouadma et al [43] et suggèrent que les moyens de prévention auraient plus d'impact s'ils sont mis en place rapidement dès la mise en place de la VM. La colonisation durant les 48 premières heures de VM avec *P. aeruginosa* multi résistants double le risque de la survenue de PAVM précoce, ceci serait dû au fait que l'antibiothérapie instaurée précocement engendrerait une pression de sélection positive. Il a déjà été montré l'impact de la colonisation à *P aeruginosa* dans le risque d'infection liée aux soins [65]. L'utilisation précoce d'antibiotique à large spectre chez les patients ventilés mécaniquement explique probablement l'impact de la colonisation à *P aeruginosa* résistant. De même, une colonisation par le SARM entre le 3ème et le 6ème jour de VM était associée à une augmentation de 50% du risque de survenue d'une PAVM tardive.

L'impact protecteur de l'antibiothérapie initiale n'est retrouvé que pour les PAVM précoces. L'impact des antibiothérapies sur le risque de PAVM tardive est plus contrasté. Seules

les fluoroquinolones prises entre le 3ème et le 6ème jour de VM diminuent le risque. A l'opposé, l'utilisation des autres antibiotiques à large spectre augmente le risque de PAVM tardives.

Concernant les apports nutritionnels entéraux, cette étude confirme l'impact délétère de la nutrition entérale pour les PAVM précoces où l'inhalation joue un grand rôle. Inversement, la nutrition n'a pas d'effet sur le risque de PAVM tardives. Les résultats plus détaillés sont rapportés dans l'article.

2) Article 2 (publié, Plos one)

PLOS | ONE

RESEARCH ARTICLE

Respective impact of implementation of prevention strategies, colonization with multiresistant bacteria and antimicrobial use on the risk of early- and late-onset VAP: An analysis of the OUTCOMEREA network

Wafa Ibn Saied[1,2], Bertrand Souweine[3], Maité Garrouste-Orgeas[4], Stéphane Ruckly[1], Michael Darmon[5], Sébastien Bailly[1,6], Yves Cohen[7], Elie Azoulay[8], Carole Schwebel[2], Aguila Radjou[9], Hatem Kallel[10], Christophe Adrie[11], Anne-Sylvie Dumenil[12], Laurent Argaud[13], Guillaume Marcotte[14], Samir Jamali[15], Laurent Papazian[16], Dany Goldgran-Toledano[17], Lila Bouadma[9], Jean-Francois Timsit[1,9]*, for the OUTCOMEREA study group[¶]

1 UMR 1137 - IAME Team 5 – DeSCID: Decision SCiences in Infectious Diseases, control and care, Inserm/Paris Diderot University, Sorbonne Paris Cité, Paris, France, **2** Medical Intensive care unit, Grenoble University Hospital, Grenoble 1 University, U823, La Tronche, France, **3** Medical Intensive Care Unit, Gabriel Montpied University Hospital, Clermont-Ferrand, France, **4** Intensive Care Unit, Saint Joseph Hospital Network, Paris, France, **5** Saint Etienne University Hospital, Medical Intensive Care Unit, Saint-Etienne, France, **6** Grenoble Alpes University, U823, Rond-point de la Chantourne, La Tronche France, **7** AP-HP, Avicenne Hospital, Intensive Care Unit, Paris and Medicine University, Paris 13 University, Bobigny, France, **8** Medical Intensive Care Unit, AP-HP, Saint Louis Hospital, Paris, France, **9** AP-HP, Bichat Hospital, Medical and infectious diseases Intensive Care Unit, Paris Diderot university, Paris, France, **10** Medical Surgical ICU, Centre hospitalier de Cayenne, Guyane, France, **11** Physiology department, Cochin University Hospital, Sorbonne Cite, Paris, France, **12** AP-HP, Antoine Béclère University Hospital, Medical-surgical Intensive Care Unit, Clamart, France, **13** Medical Intensive Care Unit, Lyon University Hospital, Lyon, France, **14** Surgical ICU, Edouard Herriot University Hospital, Lyon, France, **15** Critical care Medicine Unit Dourdan Hospital, Dourdan, France, **16** Respiratory and infectious diseases ICU, APHM Hôpital Nord, Aix Marseille University, Marseille, France, **17** Gonesse Hospital, Intensive Care Unit, Gonesse, France

¶ Membership of the OUTCOMEREA study group is provided in the Acknowledgments.
* Jean-francois.timsit@bch.aphp.fr

Check for updates

OPEN ACCESS

Citation: Ibn Saied W, Souweine B, Garrouste-Orgeas M, Ruckly S, Darmon M, Bailly S, et al. (2017) Respective impact of implementation of prevention strategies, colonization with multiresistant bacteria and antimicrobial use on the risk of early- and late-onset VAP: An analysis of the OUTCOMEREA network. PLoS ONE 12(11): e0187791. https://doi.org/10.1371/journal.pone.0187791

Editor: Yu Ru Kou, National Yang-Ming University, TAIWAN

Received: November 7, 2016

Accepted: October 26, 2017

Published: November 29, 2017

Copyright: © 2017 Ibn Saied et al. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Data Availability Statement: All relevant data are within the paper and its Supporting Information files.

Funding: The study was entirely funded by the OUTCOMEREA research network. The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Abstract

Rationale

The impact of prevention strategies and risk factors for early-onset (EOP) versus late-onset (LOP) ventilator-associated pneumonia (VAP) are still debated.

Objectives

To evaluate, in a multicenter cohort, the risk factors for EOP and LOP, as the evolution of prevention strategies.

Methods

7,784 patients with mechanical ventilation (MV) for at least 48 hours were selected into the multicenter prospective OUTCOMEREA database (1997–2016). VAP occurring between

Competing interests: The authors have declared that no competing interests exist.

the 3rd and 6th day of MV defined EOP, while those occurring after defined LOPs. We used a Fine and Gray subdistribution model to take the successful extubation into account as a competing event.

Measurements and main results

Overall, 1,234 included patients developed VAP (EOP: 445 (36%); LOP: 789 (64%)). Male gender was a risk factor for both EOP and LOP. Factors specifically associated with EOP were admission for respiratory distress, previous colonization with multidrug-resistant *Pseudomonas aeruginosa*, chest tube and enteral feeding within the first 2 days of MV. Antimicrobials administrated within the first 2 days of MV were all protective of EOP. ICU admission for COPD exacerbation or pneumonia were early risk factors for LOP, while imidazole and vancomycin use within the first 2 days of MV were protective factors. Late risk factors (between the 3rd and the 6th day of MV) were the intra-hospital transport, PAO2-FIO2<200 mmHg, vasopressor use, and known colonization with methicillin-resistant *Staphylococcus aureus*. Among the antimicrobials administered between the 3rd and the 6th day, fluoroquinolones were the solely protective one.Contrarily to LOP, the risk of EOP decreased across the study time periods, concomitantly with an increase in the compliance with bundle of prevention measures.

Conclusion

VAP risk factors are mostly different according to the pneumonia time of onset, which should lead to differentiated prevention strategies.

Introduction

Ventilator-acquired pneumonia (VAP) is defined as pneumonia arising after at least 48 hours of mechanical ventilation (MV). VAP represents the leading type of nosocomial infection in intensive care units (ICUs); its rate ranges from 8 to 25% among mechanically ventilated patients [1]. VAP is associated with a significant increase in the mortality risk for ICU patients, from 3 to 8% when using new statistical model for causal inference [2, 3]. It increases the length of ICU stay by up to 9 days [1].

The major route for acquiring VAP is oropharyngeal colonization by the endogenous flora or by pathogens acquired exogenously from the intensive care unit environment, especially the hands of health-care workers or the contaminated respiratory equipment. The stomach represents a potential site of secondary colonization and reservoir of nosocomial Gram-negative bacilli. On endotracheal-tube, the formation of biofilm may play a contributory role in sustaining tracheal colonization, paving the way for VAP mostly caused by resistant organisms such as methicillin-resistant *staphylococcus aureus* (MRSA) and non-fermentative gram-negative bacilli (GNB). The immunoparalysis occurring after the initial phase of resuscitation may also play a role in decreasing resistance to infections [4–6]

The changes in the pathogenesis of VAP over time have led to differentiate early-onset pneumonia (EOP) from late-onset pneumonia (LOP) [7]. Time-points used for differentiating them are slightly different according to studies, from >3 to ≥7 days of mechanical ventilation [8–10].

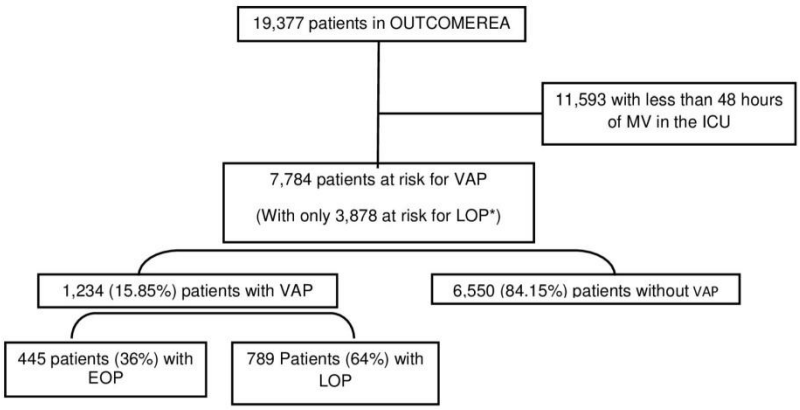
According to the differences in the pathogenesis, different preventive measures might be implemented. Indeed, the rapid decrease in the endogenous flora inoculum at the early phase of ventilation by antimicrobial prophylaxis [11], selective digestive and oral decontamination, subglottic aspiration [12, 13], semi-recumbent position [14], decreased the risk of EOP, but have no or a moderate impact on LOP. When preventive bundles such as weaning trials, orogastric tubes, semi-recumbent position, or oral care were applied, the decrease in VAP rates was greatest for the period within 5 days after ICU admission and MV initiation, suggesting that preventive measures were more effective when implemented early[6]. On the opposite, it was shown that the constitution of a secondary reservoir in the stomach promotes infections occurring later that might be partly prevented by the preservation of a low gastric pH [15].

The aim of our study was to assess specific risk factors for EOP and for LOP in a large multicenter database, and the impact of the progressive implementation of recommended preventive strategies on the rates of onset of EOP and of LOP.

Methods

Study design and data source

We conducted a retrospective analysis using data prospectively entered into a multicenter database from January 1997 to March 2016 (OUTCOMEREA database). The database is fed by 22 different French ICUs, and contains data on admission features and diagnosis, daily disease severity, iatrogenic events, nosocomial infections, and vital status. ICU units participating in the OUTCOMEREA database used a range of methods to include patients. Some ICUs included all consecutive patients, while other units included patients admitted at predefined periods of the year, and some other picked patients in certain beds that were randomly selected, without considering patient's characteristics such as the diseases at ICU admission or their medical history [16]. All patients with MV lasting more than 48 hours were included into the study. Patients were censored after 28 days of MV or death (Fig 1). Risk factors were



EOP: early onset pneumonia; LOP: Late onset pneumonia; VAP: ventilator-associated pneumonia / * having MV at least for 7 days or more

Fig 1. Flowchart.

https://doi.org/10.1371/journal.pone.0187791.g001

evaluated for the first episode of EOP on the individuals under mechanical ventilation for more than 2 days, and a similar analysis was performed for the first episode of LOP on the patients who were still mechanically ventilated on the 7th day.

Ethical issues. This study was approved by our institutional review board (CECIC Clermont-Ferrand—IRB n°5891; Ref: 2007–16), which waived the need for signed informed consent of the participants, in accordance with French legislation on non-interventional studies. However, the patients and their next of kin were asked whether they were willing to participate in the database, and none declined participation.

Population definitions. The diagnosis of VAP was suspected in patients who had received at least 48 hours of MV and developed a new or persistent infiltrate on chest radiography, associated with one of the following criteria: (1) purulent tracheal secretions, (2) fever greater than or equal to 38.5°C or hypothermia less than or equal to 36.5°C, and (3) leukocytosis greater than 10^9 cells/L or leukopenia less than 4.10^8 cells/L. The diagnosis of VAP was confirmed by a positive quantitative culture of a respiratory sample: bronchoalveolar lavage fluid (significant threshold: $\geq 10^4$cfu/ml) or plugged telescopic catheter (significant threshold: $\geq 10^3$cfu/ml) or quantitative endotracheal aspirate (significant threshold, $\geq 10^5$ cfu/ml). The model was only based on confirmed VAPs with a positive result after bacteriological culture. When VAP was suspected, samples were performed prior to any changes in the antibiotic therapy.

We chose a cut-off point at day 7 of MV. EOP was defined as the occurrence of VAP between the 3rd and the 6th day of MV. LOP was defined as the occurrence of VAP after the 6th day of MV.

A new episode of VAP was defined either by: (1) the same causative microorganism after a time interval of at least 5 days from the previous episode; (2) the acquisition of resistance of the same pathogen; or (3) a different pathogen regardless the acquisition day. Positive samples for fungi or viruses were not considered.

We also recorded data on previous carriage or colonization with MDR bacteria: multidrug-resistant *P. aeruginosa* (MDRPA), MRSA, extended-spectrum β-lactamase producing *Enterobacteriaceae* (ESBLE), and *A. baumannii*. A patient was considered as colonized with MDR bacteria if one of these 4 microorganisms was isolated from clinically-indicated samples, or from samples drawn for systematic detection for MRSA and ESBLE, i.e., samples collected at admission and weekly, from nasal and rectal swabs for MRSA and ESBLE, respectively. If confirmed, patient was considered as carrier throughout the full study period.

Data collection. The following data were collected at admission, and daily if appropriate: age; sex; comorbidities (assessed according to the Acute Physiology and Chronic Health Evaluation II definitions); severity of illness at ICU admission and daily during the ICU stay (assessed using the Simplified Acute Physiology Score II and the Logistic Organ Dysfunction score); admission category (medical, surgery, or monitoring); admission diagnosis; whether the patient was transferred from a hospital ward (defined as a stay in an acute-bed ward lasting>24 h immediately before ICU admission); lengths of ICU stay and hospital stay; and vital status at discharge from the ICU and from the hospital. Data on invasive procedures (placement of an arterial or central venous catheter, and endotracheal intubation), treatments of organ failures (catecholamine infusion, mechanical ventilation, renal replacement therapy), colonization with ESBLE, MDRPA and MRSA, and antibiotic use were also captured daily.

Prevention bundle applied during each of the study periods: before 2001, between 2001 and 2006 and after 2006, was recorded using questionnaires filled by investigators (see description in S1 Table). The compliance with prevention protocols was not monitored. We described EOP and LOP tendency taking account of the modification of bundles over these 3 periods.

Statistical analysis. Characteristics of patients and VAP episodes were described using frequency and percentage for qualitative variables, median, and interquartile range (IQR) for quantitative variables. Standard survival analyses are affected by the time of onset of the event of interest. Patients who have not experienced the event at the end of follow-up were censored. To determine the risk of an event occurrence at a certain time-point, a fundamental assumption is that such censoring is not associated with an altered chance of the event occurring at any given moment. In this study, the event of interest is the onset of pneumonia in patients with MV and followed up until day 28 or until extubation for more than 48 hours. Indeed, death and extubation for more than 48 hours is a competing event since, by definition, extubation precludes the observation of a ventilator-associated infection [17]. Risk factors of VAP (EOP and LOP) occurrence were identified separately using Fine and Gray models stratified by ICU. A multivariate model was built by including risk factors (at admission, the 2 first days of MV for EOP, and between the third and the sixth day of MV for LOP) that met the 20% significance threshold in univariate analysis. SAPS II at the beginning of mechanical ventilation period was selected for the model, instead of organ failure scores and age. Then, a backward selection process was applied until all remaining factors met the 5% threshold in the multivariate context. For EOP as for LOP, some factors are specific to the patient, such as the male gender; others were recorded at ICU admission, and others emerged later on, up to the 3rd to the 6th day after MV initiation for LOP. Sensitivity Analysis was also performed by varying MV cut-off to five days for the definition of EOP and LOP without modification in the final model (S2 Table). All models were stratified by centers and adjusted on time periods and SAPS II at the beginning of mechanical ventilation period that correspond to the main changes in prevention strategies. Results were given as subdistribution hazard ratios (sHR) and 95% confidence intervals (CI). Using P values less than 0.05 were considered as significant. As it is an exploratory trial, p-values were further corrected for multiple comparisons using the Benjamini-Hochberg procedure, as implemented in the MULTITEST procedure in SAS. Statistical analysis was performed using SAS 9.4 (Cary, NC).

Results

Overall, 7,784 ICU patients with mechanically ventilation for more than 48 hours were included *(see CONSORT flowchart*, Fig 1*)*, including 1,234 (15.85%) patients who developed VAP within the first 28 days of MV. Among them, 445 (36%) developed an EOP, and 789 (64%) developed a LOP. Characteristics at ICU admission, during the first 48 hours of MV and between the third day of MV and the sixth day of MV for patients at risk for EOP and LOP are described in Tables 1 and 2 respectively. The main causative pathogens according to the type of VAP are described in Table 3.

Incidence of EOP, but not of LOP, decreased with the study time periods. Risk factors selected separately for EOP and LOP at the final step of the multivariate models are reported on Table 4. Male gender was the only risk factor common for EOP and LOP.

Factors that may lead to a decreased bronchial clearance or aspiration such as early enteral feeding or presence of a chest tube were only associated with EOP. On the contrary, severe organ dysfunction (low PaO2:FiO2 ratio) was associated with LOP.

Most antibacterial agents used within the first 48 hours of MV protected against EOP.The early administration of Vancomycin and imidazole, and fluoroquinolones administered between day 3 and 6 protected from LOP.

In term of previous carriage or colonization with multi-drug resistant pathogens, colonization with MDRPA was a risk factor for EOP; whereas colonization with MRSA was a risk factor for LOP. When MRSA colonization was present on admission, it had a lower impact than

Table 1. Characteristics of study population at the ICU admission.

Variables at ICU admission	Patients at risk for EOP (N = 7,784)			Patients at risk for LOP (N = 3,878)		
	No EOP (N = 7,339)	EOP (N = 445)	P*	No LOP (N = 3,089)	LOP (N = 789)	P**
Age (#miss = 5)	64.6 [52.1; 75.8]	64.1 [51.2; 72.8]	0.09	66.6 [54.6; 76.3]	65.1 [53.2; 75.7]	0.02
Male gender	4,564 (62.2)	312 (70.1)	<.01	1,939 (62.8)	545 (69.1)	<.01
Chronic diseases at ICU admission						
Hepatic	528 (7.2)	22 (4.9)	0.07	197 (6.4)	57 (7.2)	0.39
Cardiovascular	1,049 (14.3)	67 (15.1)	0.66	491 (15.9)	110 (13.9)	0.18
Respiratory	1,182 (16.1)	78 (17.5)	0.43	587 (19)	165 (20.9)	0.23
Renal	355 (4.8)	30 (6.7)	0.07	147 (4.8)	29 (3.7)	0.19
Immunodeficiency	1,184 (16.1)	54 (12.1)	0.03	519 (16.8)	145 (18.4)	0.29
Diabetes						0.32
Complicated diabetes	333 (4.5)	19 (4.3)	0.71	144 (4.7)	39 (4.9)	
Non complicated diabetes	810 (11)	44 (9.9)		351 (11.4)	75 (9.5)	
No diabetes	6,196 (84.4)	382 (85.8)		2,594 (84)	675 (85.6)	
Diagnosis category at ICU admission (#miss = 18)						0.03
Scheduled surgery	639 (8.7)	40 (9)	0.05	242 (7.8)	65 (8.2)	
Emergency surgery	1,383 (18.8)	63 (14.2)		581 (18.8)	117 (14.8)	
Medical	5,317 (72.4)	342 (76.9)		2,266 (73.4)	607 (76.9)	
Diagnosis at ICU admission						
Septic shock	1,486 (20.2)	46 (10.3)	<.01	777 (25.2)	169 (21.4)	0.03
Other shock	1,088 (14.8)	69 (15.5)	0.70	444 (14.4)	15 (1.9)	0.56
Respiratory distress	2,172 (29.6)	157 (35.3)	0.01	1,090 (35.3)	252 (31.9)	<.01
COPD exacerbation	412 (5.6)	26 (5.8)	0.84	213 (6.9)	73 (9.3)	0.05
Coma	1,759 (24)	131 (29.4)	<.01	530 (17.2)	127 (16.1)	0.48
Pneumonia	1,507 (20.5)	105 (23.6)	0.12	773 (25)	252 (31.9)	<.01
Drug overdose	384 (5.2)	23 (5.2)	0.95	52 (1.7)	13 (1.6)	0.94

P* = p value comparing EOP and No EOP patients /P** = p value comparing LOP and No LOP patients; EOP early onset pneumonia; LOP: late onset pneumonia; MV: mechanical ventilation; COPD exacerbation = chronic obstructive pulmonary disease exacerbation; MV = mechanical ventilation; # miss: number of missing data

https://doi.org/10.1371/journal.pone.0187791.t001

MRSA colonization was acquired later on, between the 3rd and 6th day of mechanical ventilation (15/34 vs 38/179, $p<0.01$).

Varying MV cut-off to five days for the definition of EOP and LOP had no impact on the final model (S2 Table).

Discussion

Using commonly recognized definitions and quantitative bacterial samples, this study included a large multicenter population at risk for VAP, and aimed at identifying and differentiating risk factors associated with EOP and LOP, respectively. As one strategy for VAP prevention might be to decrease the involved risk factors, identifying the risk factors involved in VAP onset in each patient is critical. We used competing risk models in order to take account of the informative censor due to extubation for more than 48 hours and death. Among the mechanically-ventilated ICU patients included in our study, the incidence rate of VAP was about 19%, similar to the values reported in the literature [5, 10]. In patients with VAP, we observed rates of EOP and LOP of 40.2% and 59.8%, respectively, consistent with those observed in other studies [2, 18–20]. The distribution between EOP and LOP depends on the diagnostic method for pneumonia, and on the cut-off points used for the definition. We used a

Table 2. Characteristics of patients at risk for early and late onset pneumonia during their stay in ICU.

Characteristics	Patients at risk for EOP (N = 7,784)			Patients at risk for LOP (N = 3,878)		
	No EOP (N = 7,339)	EOP (N = 445)	P*	No LOP (N = 3,089)	LOP (N = 789)	P**
Variables within the first 48 hours of MV						
SAPSII score	48 [37; 59]	47 [37; 58]		50 [40; 60]	48 [39; 59]	
≤38	2,034 (27.7)	121 (27.2)	0.33	701 (22.7)	196 (24.8)	0.18
37–48	1,762 (24)	121 (27.2)		741 (24)	207 (26.2)	
49–59	1,716 (23.4)	106 (23.8)		837 (27.1)	193 (24.5)	
≥60	1,827 (24.9)	97 (21.8)		810 (26.2)	193 (24.5)	
Effective Glasgow†	4 [3; 8]	4 [3; 7]		4 [3; 8]	3 [3; 7]	
≤ 5	3,693 (50.3)	237 (53.3)	0.02	1,559 (50.5)	453 (57.4)	<.01
5>Glasgow<13	2,761 (37.6)	174 (39.1)		1,194 (38.7)	255 (32.3)	
≥ 13	885 (12.1)	34 (7.6)		336 (10.9)	81 (10.3)	
PAO_2.FIO2, median (IQR) (# miss = 150)						
<200mm Hg	3783 (51.5)	233 (52.4)	0.74	1766 (57.2)	515 (65.3)	<.01
≥200mm Hg	3556 (48.5)	212 (47.6)		1,364 (44.2)	274 (34.7)	
Microbial colonization						
ESBLE	186 (2.5)	11 (2.5)	0.94	98 (3.2)	22 (2.8)	0.58
MDR PA	76 (1)	9 (2)	0.05	38 (1.2)	12 (1.5)	0.52
Acinetobacter baumannii	216 (2.9)	12 (2.7)	0.76	113 (3.7)	27 (3.4)	0.75
MRSA	279 (3.8)	18 (4)	0.79	141 (4.6)	38 (4.8)	0.76
Treatments and procedures						
Unplanned extubation	200 (2.7)	13 (2.9)	0.81	59 (1.9)	19 (2.4)	0.37
Chest tube	566 (7.7)	54 (12.1)	<.01	263 (8.5)	84 (10.6)	0.06
Steroids	2,049 (27.9)	100 (22.5)	0.01	982 (31.8)	262 (33.2)	0.45
Paralytic agents	1,477 (20.1)	98 (22)	0.33	699 (22.6)	230 (29.2)	0.16
Proton Pump Inhibitors	4,526 (61.7)	250 (56.2)	0.02	1,940 (62.8)	471 (59.7)	0.11
Enteral feeding	2,320 (31.6)	177 (39.8)	<.01	1,122 (36.3)	307 (38.9)	0.18
Intra-hospital transport	2,069 (28.2)	108 (24.3)	0.07	856 (27.7)	220 (27.9)	0.92
Patient isolation	1,288 (17.6)	64 (14.4)	0.09	574 (18.6)	151 (19.1)	0.72
Antibacterial agents administration						
3rd and 4th generation cephalosporins	1,810 (24.7)	76 (17.1)	<.01	901 (29.2)	246 (31.2)	0.33
ß-lactam/ ß-lactamase inhibitor	2,691 (36.7)	135 (30.3)	<.01	1,107 (35.8)	295 (37.4)	0.09
Other penicillins	755 (10.3)	34 (7.6)	0.07	353 (11.4)	86 (10.9)	0.68
Penems	600 (8.2)	10 (2.2)	<.01	323 (10.5)	64 (8.1)	0.05
Fluoroquinolones	1,205 (16.4)	44 (9.9)	<.01	633 (20.5)	151 (19.1)	0.40
Aminoglycosides	1,784 (24.3)	51 (11.5)	<.01	914 (29.6)	202 (25.6)	0.03
Imidazole	849 (11.6)	30 (6.7)	<.01	448 (14.5)	86 (10.9)	0.71
Vancomycin	956 (13)	27 (6.1)	<.01	519 (16.8)	94 (11.9)	<.01
Other antibacterial agents	825 (11.2)	57 (12.8)	0.31	322 (10.4)	100 (12.7)	0.07
Variables between the 3 rd and the 6th days of MV						
SAPSII score	-	-		46 [37; 56]	46 [39; 57]	0.51
≤37				713 (23.1)	162 (20.5)	
37–57				1,660 (53.7)	442 (56)	
≥57				716 (23.2)	185 (23.4)	
Effective Glasgow†	-	-		6 [3; 10]	5 [3; 8]	<.01
≤ 5				1,192 (38.6)	379 (48)	
5>Glasgow<13				1484 (48)	319 (40.4)	
≥ 13				413 (13.4)	91 (11.5)	

(*Continued*)

Table 2. (*Continued*)

Characteristics	Patients at risk for EOP (N = 7,784)			Patients at risk for LOP (N = 3,878)		
	No EOP (N = 7,339)	EOP (N = 445)	P*	No LOP (N = 3,089)	LOP (N = 789)	P**
PAO_2:FIO2, median (IQR)	-	-				
<200mm Hg				1,499 (48.5)	492 (62.4)	<.01
≥200mm Hg				1,590 (51.5)	297 (37.6)	
Microbial colonization	-	-				
ESBLE				119 (3.9)	31 (3.9)	0.92
MDR PA				34 (1.1)	16 (2)	0.04
Acinetobacter baumannii				142 (4.6)	37 (4.7)	0.91
MRSA				123 (4)	44 (5.6)	0.05
Treatments and procedures	-	-				
Unplanned extubation				140 (4.5)	40 (5.1)	0.52
Chest tube				311 (10.1)	107 (13.6)	<.01
Steroids				1,132 (36.6)	309 (39.2)	0.19
Paralytic agents				429 (13.9)	179 (22.7)	<.01
Proton Pump Inhibitors				2,121 (68.7)	531 (67.3)	0.46
Enteral feeding				921 (29.8)	202 (25.6)	0.02
Intra-hospital transport				610 (19.7)	189 (24)	<.01
Patient isolation				610 (19.7)	166 (21)	0.42
Antibacterial agents administration	-	-				
3rd and 4th generation cephalosporins				989 (32)	265 (33.6)	0.40
ß-lactam/ ß-lactamase inhibitor				1,149 (37.2)	303 (38.4)	0.53
Other penicillins				533 (17.3)	146 (18.5)	0.41
Penems				411 (13.3)	85 (10.8)	0.06
Fluoroquinolones				641 (20.8)	140 (17.7)	0.06
Aminoglycosides				805 (26.1)	193 (24.5)	0.36
Imidazole				542 (17.5)	110 (13.9)	0.02
Vancomycin				549 (17.8)	127 (16.1)	0.27
Other antibacterial agents				559 (18.1)	182 (23.1)	<.01
Early-onset pneumonia				85 (9.7)	290 (8.8)	0.29

P** = p value comparing LOP and No LOP patients; ICU: intensive care unit; EOP early onset pneumonia; LOP: late onset pneumonia; MV: mechanical ventilation; SAPSII score = Simplified Acute Physiology Score within the first 48h after ICU admission;

† GLASGOW score = Glasgow coma scale within the first 48h after ICU admission—scored even in patients receiving sedation—represents the level of awakening of patients; MDRPA = multi-drug-resistant *Pseudomonas aeruginosa*; MRSA = Methicillin-resistant *Staphylococcus aureus*; ESBL-PE: extended-spectrum βlactamase producing *Enterobacteriaceae*; # miss: number of missing data

https://doi.org/10.1371/journal.pone.0187791.t002

cut-off point of ≥ 7 days of MV, and the diagnosis of pneumonia was confirmed by either proximal or distal techniques with quantitative cultures of collected specimens. Varying the MV cut-off from seven to five days for the definition of EOP and LOP keeps sHR roughly unchanged in our study (S2 Table).

We observed a decrease in EOP but not in LOP over the three study time periods, concomitantly with an increase in the compliance with bundles of prevention measures in the participating centers. It might be a chronological coincidence; however, it is in line with a previous study that suggested that a bundle of preventive measures was more effective when implemented early after MV initiation[6].

Differences in the pathogenesis of each VAP types contribute to explain the differences in responsible pathogens. In the EOP, the lung is thought to be invaded by endogenous flora

Table 3. Causative pathogens according to the type of ventilator-associated pneumonia, EOP or LOP.

Pathogens	EOP (N = 445)	LOP (N = 789)	pvalue
Staphylococcus aureus S*	100 (16.9)	141 (14.7)	0.24
Staphylococcus aureus MDR**	23 (5.1)	71 (8.8)	0.02
Staphylococcus coagulase negative /epidermis S*	18 (3.1)	48 (5)	0.06
Staphylococcus coagulase negative /epidermis MDR**	6 (1.3)	27 (3.4)	0.03
Acinetobacter baumannii	14 (2.4)	24 (2.5)	0.87
Pseudomonas aeruginosa S*	108 (18.3)	278 (29)	<.01
Pseudomonas aeruginosa MDR**	25 (5.6)	96 (11.9)	<.01
Stenotrophomonas maltophilia	14 (2.4)	42 (4.4)	0.04
Other Non fermenting Gram negative Bacteria✉	2 (0.3)	8 (0.8)	0.24
Escherichia coli S*	35 (5.9)	76 (7.9)	0.14
Escherichia coli MDR**	7 (1.6)	12 (1.5)	0.92
Klebsiella pneumoniae /Proteus spp. S*	47 (8)	70 (7.3)	0.63
Klebsiella pneumoniae / Proteus spp. MDR**	5 (1.1)	10 (1.2)	0.84
Serratia/ Citrobacter freundii/ Enterobacter cloacae S *	78 (13.2)	114 (11.9)	0.44
Serratia/ Citrobacter freundii/ Enterobacter cloacae MDR**	13 (2.9)	40 (5)	0.08
Haemophilus influenzae	58 (9.8)	36 (3.8)	<.01
Streptococcus pneumoniae	35 (5.9)	31 (3.2)	0.01
Other streptococci❖	32 (5.4)	24 (2.5)	<.01
Other pathogens ♦	49 (8.3)	67 (7)	0.34

*S: susceptible strains,

**: MDR: multi-drug resistant strains

✉Other Non fermenting GNB: *Pseudomonas putida* and other *Pseudomonas* spp.;, *Acinetobacter baumannii* ❖Other streptococci: group A streptococci, group B streptococci—Beta-haemolytical streptococci, group C streptococci; **other pathogens ♦**: other gram positive cocci, *Neisseria meningitidis*, *Moraxella catarrhalis*, other *Bacillus* spp., *Corynebacterium* spp, *Lactobacillus*, *Klebsiella* spp., *Serratia* spp., other aerobic Gram negativebacilli, *Peptostreptoccus*, *Coxiella burnetti*, *Mycoplasma pneumoniae*, *Legionella* spp, *Aspergillus fumigatus*

https://doi.org/10.1371/journal.pone.0187791.t003

resulting from direct inoculation during emergency intubation or endotracheal tube manipulation, whereas pathogens involved in LOP originate from flora modified by hospitalization and antimicrobial treatment [5, 21]. The pattern of resistance highly depends on the level of resistance of the country or hospital. In countries with high rate of MDR pathogens, the difference between rates of MDR pathogens in LOP and EOP was not significant [22, 23]. Colonization with MDR bacteria represents a risk factor for the development of VAP [24]. In our study, colonization with MDR *P. aeruginosa* within the first 48 hours of MV was associated with a twice higher occurrence of EOP compared to that observed in non-colonized patients. It may reflect the fact that antibiotic used in the first days of mechanical ventilation were most often not active against MDR *P. aeruginosa*, and may induce colonization pressure. The colonization with MRSA, especially when it was acquired between the 3rd and 6th day of mechanical ventilation, was an important risk factor of LOP, with an incidence increased by 50% [21, 25]. Other studies demonstrated that nasal colonization with *S. aureus*, including MRSA, is a risk factor for the development of VAP [18]. The mechanisms by which previous colonization increased the risk of LOP is partly related to the protective role of previous antimicrobial therapy active on other microorganisms than MRSA. It could also be related to the decrease of prevention and of control of VAP, already shown to be associated with isolation [26]. The impact of the quantitative importance of colonization and the location of colonization was not available in our database and would require further studies.

Table 4. Summary of risk factors of early- and late-onset pneumonia.

Variables	Early-Onset Pneumonia		Late-Onset Pneumonia	
	sHR	p	sHR	p
Male gender	1.33 [1.09–1.63]	<.01	1.23 [1.06–1.43]	0.0064
Chronic diseases at ICU admission				
Renal	1.49 [1.02–2.16]	0.04		
Immunodeficiency			1.27 [1.05–1.53]	0.012
Diagnosis at ICU admission				
Respiratory distress	1.28 [1.04–1.57]	0.02		
COPD exacerbation			1.24 [1.06–1.45]	0.0062
Pneumonia			1.26 [1.08–1.47]	<.01
SAPSII score (ref: ≤38)		0.25		0.0003
SAPSII ≥ 60	0.87 [0.65–1.16]	0.36	0.69 [0.57–0.84]	0.0003
48 ≤ SAPSII < 60	1.02 [0.78–1.33]	0.92	0.72 [0.59–0.88]	0.001
38 ≤ SAPSII < 48	1.15 [0.90–1.48]	0.26	0.92 [0.76–1.12]	0.393
Glasgow score†(ref:>13)		0.04		
5 ≤ Glasgow < 13	1.62 [1.10–2.36]	0.01		
Glasgow < 5	1.55 [1.06–2.27]	0.02		
Period effect (ref: <2001)		0.01		0.277
2001–2006	0.84 [0.58–1.21]	0.34	1.25 [0.95–1.64]	0.114
≥ 2007	0.63 [0.44–0.91]	0.01	1.22 [0.92–1.63]	0.161
Variables within the first 48 hours of MV				
Chest Tube	1.71 [1.30–2.26]	<.01		
MDR PA colonization	2.12 [1.08–4.16]	0.03		
Enteral feeding	1.34 [1.09–1.66]	<.01		
Antibacterial agents				
3 rd and 4 th generation cephalosporins	0.50 [0.38–0.65]	<.01		
ß lactam/ ß lactamase inhibitor	0.60 [0.48–0.75]	<.01		
Other penicillin	0.60 [0.42–0.87]	<.01		
Penems	0.27 [0.14–0.50]	<.01		
Aminoglycosides	0.57 [0.42–0.78]	<.01		
Fluoroquinolones	0.48 [0.35–0.68]	<.01		
Imidazoles			0.79 [0.63–0.99]	0.046
Vancomycin	0.62 [0.42–0.92]	0.02	0.65 [0.53–0.79]	<.0001
Variables between the 3 rd and the 6th days of MV				
Fluoroquinolones			0.65 [0.53–0.79]	<.0001
Other Antibacterial agents			1.25 [1.05–1.49]	0.011
Intra-hospital transport			1.20 [1.01–1.42]	0.037
Colonization with MRSA			1.40 [1.01–1.93]	0.040
PAO_2: FIO2 ratio <200 mmHg			1.49 [1.29–1.73]	<.0001

Variables introduced in the model of risk factor of EOP at the first step of the selection procedure were: age, male gender, chronic hepatic diseases, chronic renal diseases, immunodeficiency, diagnostic categories, septic shock. Variables within the first 48 hours of MV: chest tube, MDR PA colonization, steroids, Proton Pump Inhibitors, enteral feeding, intra-hospital transport, Patient isolation, Septic shock, Respiratory distress, coma, Aminoglycosides, 3rd and 4th generation cephalosporins, Penems, Fluoroquinolones, Vancomycin, Metronidazole, other penicillin, ß lactam/ ß lactamase inhibitor

Variables introduced in the model of risk factor of LOP at the first step of the selection procedure were: Septic shock, Respiratory distress, COPD exacerbation pneumonia, male gender, Variables within the first 48 hours of MV; chest tube, Proton Pump Inhibitors, SAPSII score Imidazole, other Antibacterial agent, Vancomycin, Penems, Aminoglycosides, Variables between the 3 rd and the 6 days of MV: PAO2FIO2, GLASGOW score, Metronidazole, other Antibacterial agent, Fluoroquinolones, Penems, intra-hospital transport, enteral feeding, vasopressor, MDR PA and MRSA colonization

ICU: intensive care unit; EOP early onset pneumonia; LOP: late onset pneumonia; MV: mechanical ventilation; SAPSII score = Simplified Acute Physiology Score within the first 48h after ICU admission;

† GLASGOW score = Glasgow coma scale within the first 48h after ICU admission—scored even in patients receiving sedation—represents the level of awakening of patients; MDRPA = multi-drug-resistant *Pseudomonas aeruginosa*; MRSA = Methicillin-resistant *Staphylococcus aureus*; ESBLE: extended-spectrum βlactamase-producing *Enterobacteriaceae*

(†) p<0.001 for comparisons between the 3 categories of Glasgow score.

https://doi.org/10.1371/journal.pone.0187791.t004

Previous antimicrobial therapy was a protective factor of EOP but had marginal impact on the risk of LOP. The administration of betalactams, aminoglycosides or fluoroquinolones within the first 48 hours of MV protected from EOP. The maximal effect was obtained with carbapenems. Early administration of vancomycin protected from LOP, as did the use of fluoroquinolones between the 3rd and the 6th day of MV. This finding is consistent with previous studies results [11, 27]. It was shown that selective digestive decontamination with topical antibiotics combined with IV antibiotics during the first days of MV also decreased VAP rate [28]. In our study, the protective effect in the EOP risk of early anti-microbial against Gram-negative bacteria is counter-balanced by the deleterious impact of MDRPA carriage within the first 48 hours of mechanical ventilation.

In ICU patients with nosocomial pneumonia, compared to ICU patients without nosocomial pneumonia, a study identified local markers of lung immunosuppression, such as prolonged low expression of HLA-DR on alveolar macrophages and low cytokine levels [29]. Authors hypothesized that the development of nosocomial pneumonia might be associated with local organ immunosuppression. This post-aggressive general and pulmonary immunoparalysis may explain why both vasopressor use and low PaO2:Fi02 ratio remained important risk factors of LOP. Coma as the diagnosis for ICU admission was not a risk factor of EOP. However, the level of consciousness assessed in our study by the level of the effective Glasgow coma scale was associated with an increased risk of EOP. Our results suggest the need for awakening patients as early as possible during the ICU stay.

The use of enteral feeding in the first 48 hours of MV was a risk factor of EOP, and had no influence on LOP, therefore confirming previous work performed on patients with shock [30]. Early enteral nutrition may favor gastric regurgitation and inhalation of gastric content in case of intolerance, which may explain this result. Stress ulcer prophylaxis is associated with microbial colonization of the gastric juice and modification of the bacterial flora of the upper respiratory tract. Our study also suggests the lack of impact of proton pump inhibitor on the risk of VAP, consistently with a recent systematic review and meta-analysis [31]. The adverse impact of intra-hospital transport on risk of LOP is consistent with previous findings [32, 33]. The decrease of availability of tracheal suction, inadequate transport ventilator or pre-transport underestimation of patient' severity of illness may lead to more frequent occurrence of atelectasis and ventilator-associated pneumonia.

Our study had some limitations. VAP diagnosis in patients is difficult, as the standard for the diagnosis of VAP remains the histological examination and culture of lung tissue. We used bronchoscopic techniques or quantitative culture of endotracheal aspirates for bacteriological confirmation of the pneumonia diagnosis. We may have had a lower VAP rate compared to studies based only on clinical evaluations; however, this should impact equally EOP and LOP. The significant decrease of EOP over the study time periods is likely related to changes in prevention measures used in the study centers, but could also be due to unmeasured confounders, since we did not monitor the individual compliance with these measures. In addition, patients with a higher SAPSII score (>60) have a non-significant protection (sHR = 0.87), and the likely explanation is that they may die before any VAP onset. Finally, the impact of MDR and antimicrobial therapy refers to MDR risk observed in France, where carbapenemase-resistant *Enterobacteriaceae* strains are rare.

The major study strength is the use of the large, multicentric OUTCOMEREA database. This database contains patient's admission information and behavior during their ICUs stay, and comprises ICUs from university and non-university hospitals. Centers use a consistent VAP definition, which facilitates the generalization of our findings. In addition, the first episode of VAP was identified using the Fine and Gray model. This model allows a simultaneous

estimation of two independent competing events: being extubated for more than 48 hours, death before occurrence of VAP.

Conclusion

Despite the limitations discussed above, our study showed important findings, particularly the impact of colonization on VAP occurrence and the protective effects of antibiotics administered during the first 48 hours of MV. Factors associated with a quantitative increase of aspiration of the oropharyngeal content were predominant for EOP. In LOP the persistence of organ system failures and shock, and colonization with MRSA were the main risk factors. VAP risk factors are mostly different according to the pneumonia time of onset, which should lead to differentiated prevention strategies.

Supporting information

S1 File.
(CSV)

S2 File.
(CSV)

S1 Table. Summary of procedures used for ventilator associated pneumonia prevention in the ICUs of the OUTCOMEREA network.
(DOCX)

S2 Table. Risk factors of early pneumonia using a cut-off at 5 days of mechanical ventilation.
(DOCX)

Acknowledgments

We want to acknowledge the help of Céline Feger, MD (EMIBiotech) for her editorial support.

Members of the outcomerea study group

***Scientific Committee*:** Jean-François Timsit (Medical and Infectious Diseases ICU, Bichat-Claude Bernard Hospital, Paris, France; UMR 1137 Inserm –Paris Diderot university IAME, F75018, Paris); Elie Azoulay (Medical ICU, Saint Louis Hospital, Paris, France); Maïté Garrouste-Orgeas (ICU, Saint-Joseph Hospital, Paris, France); Jean-Ralph Zahar (Infection Control Unit, Angers Hospital, Angers, France); Christophe Adrie (ICU, Delafontaine Hospital, Saint Denis, and Physiology, Cochin Hospital, Paris, France); Michael Darmon (Medical ICU, Saint Etienne University Hospital, St Etienne, France); and Christophe Clec'h (ICU, Avicenne Hospital, Bobigny, and UMR 1137 Inserm –Paris Diderot university IAME, F75018, Paris, France).

***Biostatistical and Information System Expertise*:** Jean-Francois Timsit (Medical and Infectious Diseases ICU, Bichat-Claude Bernard Hospital, Paris, France; UMR 1137 Inserm –Paris Diderot university IAME, F75018, Paris); Corinne Alberti (Medical Computer Sciences and Biostatistics Department, Robert Debré Hospital, Paris, France); Adrien Français (Integrated Research Center U823, Grenoble, France); Aurélien Vesin (OUTCOMEREA organization and Integrated Research Center U823, Grenoble, France); Stephane Ruckly (OUTCOMEREA organization and Inserm UMR 1137 IAME, F75018, Paris); Sébastien Bailly (Grenoble university hospital Inserm UMR 1137 IAME, F75018, Paris) and Christophe Clec'h (ICU, Avicenne

Hospital, Bobigny, and Inserm UMR 1137 IAME, F75018, Paris, France); Frederik Lecorre (Supelec, France); Didier Nakache (Conservatoire National des Arts et Métiers, Paris, France); and Aurélien Vannieuwenhuyze (Tourcoing, France).

***Investigators of the OUTCOMEREA Database*:** Christophe Adrie (ICU, Delafontaine Hospital, Saint Denis, and Physiology, Cochin Hospital, Paris, France); Bernard Allaouchiche (ICU, Pierre benite Hospital, Lyon, France); Laurent Argaud (Medical ICU, Hospices Civils de Lyon, Lyon, France); Claire Ara-Somohano (Medical ICU, University Hospital, Grenoble, France); Elie Azoulay (Medical ICU, Saint Louis Hospital, Paris, France); Francois Barbier (medical-surgical ICU, Orleans, France), Jean-Pierre Bedos (ICU, Versailles Hospital, Versailles, France); Julien Bohé (ICU, Hôpital Pierre Benite, Lyon France), Lila Bouadma (ICU, Bichat Hospital, Paris, France); Christine Cheval (ICU, Hyeres Hospital, Hyeres, France); Christophe Clec'h (ICU, Avicenne Hospital, Bobigny, France); Michael Darmon (ICU, Saint Etienne Hospital, Saint Etienne, France); Anne-Sylvie Dumenil (Antoine Béclère Hospital, Clamart, France); Claire Dupuis (Bichat hospital and UMR 1137 Inserm –Paris Diderot university IAME, F75018, Paris, France), Jean-Marc Forel (AP HM, Medical ICU, Hôpital Nord Marseille), Marc Gainier (la Timone hospital, Marseille, France), Akim Haouache (Surgical ICU, H Mondor Hospital, Creteil, France); Samir Jamali (ICU, Dourdan, Dourdan Hospital, Dourdan, France); Hatem Khallel (ICU, Cayenne General Hospital, Cayenne, France); Alexandre Lautrette (ICU, G Montpied Hospital, Clermont-Ferrand, France); Guillaume Marcotte (Surgical ICU, Hospices Civils de Lyon, Lyon, France); Eric Le Miere (ICU, Louis Mourier Hospital, Colombes, France); Maxime Lugosi (Medical ICU, University Hospital Grenoble, Grenoble, France); Bruno Mourvillier (ICU, Bichat Hospital, Paris, France); Benoît Misset (ICU, Saint-Joseph Hospital, Paris, France); Delphine Moreau (ICU, Saint-Louis Hospital, Paris, France); Bruno Mourvillier (ICU, Bichat Hospital, Paris, France); Laurent Papazian (Hopital Nord, Marseille, France), Benjamin Planquette (pulmonology ICU, George Pompidou hospital Hospital, Versailles, France); Bertrand Souweine (ICU, G Montpied Hospital, Clermont-Ferrand, France); Carole Schwebel (ICU, A Michallon Hospital, Grenoble, France); Gilles Troché (ICU, Antoine Béclère Hospital, Clamart, France); Marie Thuong (ICU, Delafontaine Hospital, Saint Denis, France); Guillaume Thierry (ICU, Saint-Louis Hospital, Paris, France); Dany Toledano (ICU, Gonesse Hospital, Gonesse, France); and Eric Vantalon (SICU, Saint-Joseph Hospital, Paris, France).

***Study Monitors*:** Julien Fournier, Caroline Tournegros, Stéphanie Bagur, Mireille Adda, Vanessa Vindrieux, Loic Ferrand, Nadira Kaddour, Boris Berthe, Samir Bekkhouche, Kaouttar Mellouk, Sylvie Conrozier, Igor Theodose, Veronique Deiler, and Sophie Letrou.

Author Contributions

Conceptualization: Wafa Ibn Saied, Jean-Francois Timsit.

Data curation: Stéphane Ruckly.

Investigation: Jean-Francois Timsit.

Methodology: Wafa Ibn Saied, Lila Bouadma, Jean-Francois Timsit.

Resources: Maité Garrouste-Orgeas, Michael Darmon, Yves Cohen, Elie Azoulay, Carole Schwebel, Aguila Radjou, Hatem Kallel, Guillaume Marcotte, Samir Jamali, Laurent Papazian, Lila Bouadma, Jean-Francois Timsit.

Software: Wafa Ibn Saied, Stéphane Ruckly, Sébastien Bailly.

Supervision: Stéphane Ruckly.

Validation: Wafa Ibn Saied, Stéphane Ruckly, Michael Darmon, Sébastien Bailly, Carole Schwebel, Jean-Francois Timsit.

Visualization: Bertrand Souweine, Aguila Radjou, Christophe Adrie, Anne-Sylvie Dumenil, Laurent Argaud, Dany Goldgran-Toledano, Lila Bouadma.

Writing – original draft: Wafa Ibn Saied.

Writing – review & editing: Jean-Francois Timsit.

References

1. Chastre J, Fagon JY. Ventilator-associated pneumonia. Am J Respir Crit Care Med. 2002; 165(7):867–903. Epub 2002/04/06. https://doi.org/10.1164/ajrccm.165.7.2105078 PMID: 11934711.
2. Bekaert M, Timsit JF, Vansteelandt S, Depuydt P, Vesin A, Garrouste-Orgeas M, et al. Attributable mortality of ventilator-associated pneumonia: a reappraisal using causal analysis. Am J Respir Crit Care Med. 2011; 184(10):1133–9. Epub 2011/08/20. https://doi.org/10.1164/rccm.201105-0867OC PMID: 21852541.
3. Nguile-Makao M, Zahar JR, Francais A, Tabah A, Garrouste-Orgeas M, Allaouchiche B, et al. Attributable mortality of ventilator-associated pneumonia: respective impact of main characteristics at ICU admission and VAP onset using conditional logistic regression and multi-state models. Intensive Care Med. 2010; 36(5):781–9. https://doi.org/10.1007/s00134-010-1824-6 PMID: 20232046.
4. Hotchkiss RS, Monneret G, Payen D. Sepsis-induced immunosuppression: from cellular dysfunctions to immunotherapy. Nat Rev Immunol. 2013; 13(12):862–74. https://doi.org/10.1038/nri3552 PMID: 24232462
5. Giard M, Lepape A, Allaouchiche B, Guerin C, Lehot JJ, Robert MO, et al. Early- and late-onset ventilator-associated pneumonia acquired in the intensive care unit: comparison of risk factors. J Crit Care. 2008; 23(1):27–33. Epub 2008/03/25. https://doi.org/10.1016/j.jcrc.2007.08.005 PMID: 18359418.
6. Bouadma L, Deslandes E, Lolom I, Le Corre B, Mourvillier B, Regnier B, et al. Long-term impact of a multifaceted prevention program on ventilator-associated pneumonia in a medical intensive care unit. Clin Infect Dis. 2010; 51(10):1115–22. https://doi.org/10.1086/656737 PMID: 20936973
7. Mandelli M, Mosconi P, Langer M, Cigada M. Is pneumonia developing in patients in intensive care always a typical "nosocomial" infection? Lancet. 1986; 2(8515):1094–5. Epub 1986/11/08. PMID: 2877241.
8. Akca O, Koltka K, Uzel S, Cakar N, Pembeci K, Sayan MA, et al. Risk factors for early-onset, ventilator-associated pneumonia in critical care patients: selected multiresistant versus nonresistant bacteria. Anesthesiology. 2000; 93(3):638–45. Epub 2000/09/02. PMID: 10969295.
9. Nseir S, Di Pompeo C, Pronnier P, Soubrier S, Onimus T, Saulnier F, et al. [Early and late nosocomial broncho-pulmonary diseases in intensive care. Comparative study of risk factors and of causing bacteria]. Presse Med. 2003; 32(24):1111–5. Epub 2003/09/02. PMID: 12947739.
10. Trouillet JL, Chastre J, Vuagnat A, Joly-Guillou ML, Combaux D, Dombret MC, et al. Ventilator-associated pneumonia caused by potentially drug-resistant bacteria. Am J Respir Crit Care Med. 1998; 157(2):531–9. Epub 1998/02/26. https://doi.org/10.1164/ajrccm.157.2.9705064 PMID: 9476869.
11. Valles J, Peredo R, Burgueno MJ, Rodrigues de Freitas AP, Millan S, Espasa M, et al. Efficacy of single-dose antibiotic against early-onset pneumonia in comatose patients who are ventilated. Chest. 2013; 143(5):1219–25. Epub 2013/05/30. https://doi.org/10.1378/chest.12-1361 PMID: 23715136.
12. Lacherade JC, De Jonghe B, Guezennec P, Debbat K, Hayon J, Monsel A, et al. Intermittent subglottic secretion drainage and ventilator-associated pneumonia: a multicenter trial. Am J Respir Crit Care Med. 2010; 182(7):910–7. https://doi.org/10.1164/rccm.200906-0838OC PMID: 20522796
13. Mao Z G L, Wang G, et al. Subglottic secretion suction for preventing ventilator-associated pneumonia: an updated meta-analysis and trial sequential analysis. Critical Care. 2016; 20. https://doi.org/10.1186/s13054-016-1527-7 PMID: 27788682
14. Drakulovic MB, Torres A, Bauer TT, Nicolas JM, Nogue S, Ferrer M. Supine body position as a risk factor for nosocomial pneumonia in mechanically ventilated patients: a randomised trial. Lancet. 1999; 354(9193):1851–8. https://doi.org/10.1016/S0140-6736(98)12251-1 PMID: 10584721
15. Prod'hom G, Leuenberger P, Koerfer J, et al. Nosocomial pneumonia in mechanically ventilated patients receiving antacid, ranitidine, or sucralfate as prophylaxis for stress ulcer: A randomized controlled trial. Annals of Internal Medicine. 1994; 120(8):653–62. https://doi.org/10.7326/0003-4819-120-8-199404150-00005 PMID: 8135449

16. Lautrette A G-O M, Bertrand PM, Goldgran-Toledano D, Jamali S, Laurent V, Argaud L, Schwebel C, Mourvillier B, Darmon M, Ruckly S, Dumenil AS, Lemiale V, Souweine B, Timsit JF; Outcomerea Study Group. Respective impact of no escalation of treatment, withholding and withdrawal of life-sustaining treatment on ICU patients' prognosis: a multicenter study of the Outcomerea Research Group. Intensive Care Med 2015; 41():1763–72. https://doi.org/10.1007/s00134-015-3944-5 PMID: 26149302

17. Wolkewitz M, Cooper BS, Bonten MJM, Barnett AG, Schumacher M. Interpreting and comparing risks in the presence of competing events. BMJ: British Medical Journal. 2014; 349. https://doi.org/10.1136/bmj.g5060 PMID: 25146097

18. Martin-Loeches I, Deja M, Koulenti D, Dimopoulos G, Marsh B, Torres A, et al. Potentially resistant microorganisms in intubated patients with hospital-acquired pneumonia: the interaction of ecology, shock and risk factors. Intensive Care Med. 2013; 39(4):672–81. Epub 2013/01/30. https://doi.org/10.1007/s00134-012-2808-5 PMID: 23358539.

19. Muscedere JG, Martin CM, Heyland DK. The impact of ventilator-associated pneumonia on the Canadian health care system. J Crit Care. 2008; 23(1):5–10. https://doi.org/10.1016/j.jcrc.2007.11.012 PMID: 18359415.

20. Vanhems P, Lepape A, Savey A, Jambou P, Fabry J. Nosocomial pulmonary infection by antimicrobial-resistant bacteria of patients hospitalized in intensive care units: risk factors and survival. J Hosp Infect. 2000; 45(2):98–106. Epub 2000/06/22. https://doi.org/10.1053/jhin.2000.0752 PMID: 10860686.

21. Bassetti M, Taramasso L, Giacobbe DR, Pelosi P. Management of ventilator-associated pneumonia: epidemiology, diagnosis and antimicrobial therapy. Expert Rev Anti Infect Ther. 2012; 10(5):585–96. Epub 2012/06/19. https://doi.org/10.1586/eri.12.36 PMID: 22702322.

22. Restrepo MI, Peterson J, Fernandez JF, Qin Z, Fisher AC, Nicholson SC. Comparison of the bacterial etiology of early-onset and late-onset ventilator-associated pneumonia in subjects enrolled in 2 large clinical studies. Respir Care. 2013; 58(7):1220–5. Epub 2013/01/12. https://doi.org/10.4187/respcare.02173 PMID: 23307825

23. Giantsou E, Liratzopoulos N, Efraimidou E, Panopoulou M, Alepopoulou E, Kartali-Ktenidou S, et al. Both early-onset and late-onset ventilator-associated pneumonia are caused mainly by potentially multiresistant bacteria. Intensive Care Med. 2005; 31(11):1488–94. Epub 2005/09/10. https://doi.org/10.1007/s00134-005-2697-y PMID: 16151723.

24. Rocha LA, Marques Ribas R, da Costa Darini AL, Gontijo Filho PP. Relationship between nasal colonization and ventilator-associated pneumonia and the role of the environment in transmission of Staphylococcus aureus in intensive care units. Am J Infect Control. 2013; 41(12):1236–40. Epub 2013/07/31. https://doi.org/10.1016/j.ajic.2013.04.009 PMID: 23890377.

25. Rello J, Chastre J, Cornaglia G, Masterton R. A European care bundle for management of ventilator-associated pneumonia. J Crit Care. 2011; 26(1):3–10. Epub 2010/06/12. https://doi.org/10.1016/j.jcrc.2010.04.001 PMID: 20537504.

26. Zahar JR, Garrouste-Orgeas M, Vesin A, Schwebel C, Bonadona A, Philippart F, et al. Impact of contact isolation for multidrug-resistant organisms on the occurrence of medical errors and adverse events. Intensive Care Med. 2013; 39(12):2153–60. Epub 2013/09/03. https://doi.org/10.1007/s00134-013-3071-0 PMID: 23995982.

27. Bornstain C, Azoulay E, De Lassence A, Cohen Y, Costa MA, Mourvillier B, et al. Sedation, sucralfate, and antibiotic use are potential means for protection against early-onset ventilator-associated pneumonia. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 2004; 38(10):1401–8. Epub 2004/05/25. https://doi.org/10.1086/386321 PMID: 15156478.

28. de Smet AM, Kluytmans JA, Cooper BS, Mascini EM, Benus RF, van der Werf TS, et al. Decontamination of the digestive tract and oropharynx in ICU patients. The New England journal of medicine. 2009; 360(1):20–31. Epub 2009/01/02. https://doi.org/10.1056/NEJMoa0800394 PMID: 19118302.

29. Muehlstedt SG, Lyte M, Rodriguez JL. Increased IL-10 production and HLA-DR suppression in the lungs of injured patients precede the development of nosocomial pneumonia. Shock. 2002; 17(6):443–50. Epub 2002/06/19. PMID: 12069178.

30. Reignier J, Darmon M, Sonneville R, Borel AL, Garrouste-Orgeas M, Ruckly S, et al. Impact of early nutrition and feeding route on outcomes of mechanically ventilated patients with shock: a post hoc marginal structural model study. Intensive Care Med. 2015; 41(5):875–86. Epub 2015/03/21. https://doi.org/10.1007/s00134-015-3730-4 PMID: 25792207.

31. Krag M, Perner A, Wetterslev J, Wise MP, Hylander Moller M. Stress ulcer prophylaxis versus placebo or no prophylaxis in critically ill patients. A systematic review of randomised clinical trials with meta-analysis and trial sequential analysis. Intensive Care Med. 2014; 40(1):11–22. Epub 2013/10/22. https://doi.org/10.1007/s00134-013-3125-3 PMID: 24141808.

32. Schwebel C, Clec'h C, Magne S, Minet C, Garrouste-Orgeas M, Bonadona A, et al. Safety of intrahospital transport in ventilated critically ill patients: a multicenter cohort study*. Critical care medicine.

2013; 41(8):1919–28. Epub 2013/07/19. https://doi.org/10.1097/CCM.0b013e31828a3bbd PMID: 23863225.

33. Bercault N, Wolf M, Runge I, Fleury JC, Boulain T. Intrahospital transport of critically ill ventilated patients: a risk factor for ventilator-associated pneumonia—a matched cohort study. Crit Care Med. 2005; 33(11):2471–8. Epub 2005/11/09. PMID: 16276168.

Chapitre 2 : Comparaison des pneumonies acquises sous ventilation mécanique et hors ventilation mécanique en réanimation : facteurs de risque et mortalité attribuable.

1) Résumé

Les pneumopathies acquises en réanimation diffèrent selon la présence ou pas de la VM invasive. Cependant la majorité des articles se basent sur les données recueillies pour les PAVM et les extrapolent pour les ICU-HAP en réanimation. Ceci a motivé la réalisation de cette étude afin de déterminer dans quelle mesure ces projections sont fondées.

Nous avons donc étudié les PAVM et les pneumonies acquises en réanimation en dehors de la ventilation (ICU-HAP).

Pour déterminer les facteurs de risque de décès en réanimation, un modèle de Cox avec la pneumopathie comme variable temps dépendante a été utilisé. L'analyse a pris en compte les évènements successifs pour un même malade dans les périodes de risque de ICU-HAP et dans les périodes à risque de PAVM. Une analyse de sous-groupe selon la pathogénicité des germes était prévue. Nos résultats ont fait l'objet d'un article publié dans *Critical care medecine*. Au niveau de la base de données OUTCOMEREA, 14 212 patients sont hospitalisés plus de 48H en réanimation, ce qui nous a permis d'avoir 7 735 patients à risque d'une PAVM et 9 747 patients à risque pour une HAP. Certains patients étaient successivement à risque pour les 2 types de pneumopathies lors de leur séjour en réanimation : 3 270 patients.

Pendant les périodes d'étude nous avons observé 176 épisodes d'ICU-HAP et 1 161 épisodes de PAVM (correspondant à une incidence de 3.2 pour 1000 jours-patients vs 21 pour 1000 jours de ventilation mécanique). Les germes les plus souvent retrouvés sont : *S. aureus, P. aeruginosa*, et entérobactéries avec une répartition similaire dans les 2 groupes, confirmant ainsi les données microbiologiques, et démontrant une similitude des pathogènes responsables des pneumopathies en réanimation indépendamment de la présence de VM ainsi que sa durée[66]. L'adéquation lors

des 24 premières heures de survenue de la pneumopathie était de 73% chez les patients avec une ICU-HAP et de 69 % pour les patients avec une PAVM. La PAVM est un facteur indépendant de mortalité dans notre étude avec un HR de 1.52 [1.27–1.82] dans le groupe non traité adéquatement vs 1.31 [1.16–1.48] dans le groupe traité adéquatement. Fait inédit, l'évaluation du sur-risque de décès induit par les ICU-HAP était de 82% (HR 1.82 [1.35–2.45]) plus élevé que celui observé pour les PAVM. L'adéquation de l'antibiothérapie pour ce groupe ne modifiait pas le sur-risque de décès. L'absence d'impact de l'antibiothérapie adéquate dans le groupe ICU-HAP peut être expliquée par la sélection d'un groupe plus sévère d'ICU-HAP du fait de la nécessité d'une bactériologie positive. Il peut aussi suggérer que le diagnostic est réalisé trop tardivement au stade ou la réversibilité est moindre. Enfin, certains diagnostics ont pu être portés par excès rendant illusoire l'efficacité d'un traitement antibiotique, ou par défaut, du fait de l'absence de prélèvement bactériologiques avant changement des antibiotiques ou de l'absence de recherche systématique d'infections virales.

Le diagnostic positif des PAVM et des ICU-HAP est en effet très complexe. Dans une analyse systématique des études interventionnelles, nous avons montré que les critères de suspicion de pneumonies nosocomiales en réanimation chez les sujets non ventilés sont mal codifiés, et hétérogènes en fonction des études publiées. Seulement 55% des études publiées exigeaient la réalisation d'un prélèvement bactériologique pour faire le diagnostic (**Article n°4**).

En dehors des essais randomisés, une étude récente [67] confirme d'ailleurs que les prélèvements bactériologiques diagnostiques sont bien moins souvent réalisés en cas de pneumonies nosocomiales survenant chez le sujet non-ventilé.

2) Article 3 (publié, Critical care medecine)

A Comparison of the Mortality Risk Associated With Ventilator-Acquired Bacterial Pneumonia and Nonventilator ICU-Acquired Bacterial Pneumonia*

Wafa Ibn Saied, MD[1–3]; Bruno Mourvillier, MD[1,4]; Yves Cohen, MD[5,6]; Stephane Ruckly, MSc[1,7]; Jean Reignier, MD, PhD[8]; Guillaume Marcotte, MD[9]; Shidasp Siami, MD, PhD[10]; Lila Bouadma, MD, PhD[1,4]; Michael Darmon, MD, PhD[11,12]; Etienne de Montmollin, MD[13]; Laurent Argaud, MD, PhD[14]; Hatem Kallel, MD[15]; Maité Garrouste-Orgeas, MD[1,16,17]; Lilia Soufir, MD[16,17]; Carole Schwebel, MD, PhD[18]; Bertrand Souweine, MD, PhD[19]; Dany Glodgran-Toledano, MD[20]; Laurent Papazian, MD, PhD[21]; Jean-François Timsit, MD, PhD[1,4,7]; on behalf of the OUTCOMEREA Study Group

Downloaded from http://journals.lww.com/ccmjournal by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8KKGKV0Ymy+78= on 03/04/2019

*See also p. 472.

[1]UMR 1137, IAME, Université Paris Diderot, Paris, France.
[2]Departement of Emergency, AP-HP, Henri Mondor Hospital, Paris, France.
[3]Emergency Department, Henri Mondor Hospital, Medicine University Paris-Est Créteil Val de Marne, France.
[4]Medical and Infectious Diseases Intensive Care Unit, AP-HP, Bichat Hospital, Paris Diderot University, Paris, France.
[5]Intensive Care Unit, AP-HP, Avicenne Hospital, Paris, France.
[6]Intensive Care Unit, Medicine University, Paris 13 University, Bobigny, France.
[7]Outcomerea Research Network, Aulnay sous Bois, France.
[8]Medical Intensive Care Unit and University Hospital Centre, Nantes, France.
[9]Surgical Intensive Care Unit and Lyon University Hospital, Lyon, France.
[10]Critical Care Medicine Unit, CH Etampes-Dourdan, Etampes, France.
[11]Medical Intensive Care Unit, Saint Etienne University Hospital, Saint-Etienne, France.
[12]Intensive Care Unit, Jacques Lisfranc Medicine University, Jean Monnet University, Saint-Etienne, France.
[13]CH de Saint-Denis – Hôpital Delafontaine Service de Réanimation Polyvalente, Saint-Denis, Cedex, France.
[14]Medical ICU, Edouard Herriot University Hospital, Lyon, France.
[15]Medical Surgical ICU, Centre Hospitalier de Cayenne, Cayenne, French Guiana.
[16]Intensive Care Unit, Saint Joseph Hospital Network, Paris, France.
[17]Intensive Care Unit, Medicine University, Paris Descartes University, Sorbonne Cite, Paris, France.
[18]Medical Intensive Care Unit, Grenoble University Hospital, Grenoble 1 University, La Tronche, France.
[19]Medical Intensive Care Unit, Gabriel Montpied University Hospital, Clermont-Ferrand, France.
[20]Medical-Surgical Intensive Care Unit, Le Raincy-Montfermeil General hospital, France.
[21]Respiratory and infectious diseases ICU, APHM Hôpital Nord, Aix Marseille University, Marseille, France.

Copyright © 2018 by the Society of Critical Care Medicine and Wolters Kluwer Health, Inc. All Rights Reserved.

DOI: 10.1097/CCM.0000000000003553

The members of the OUTCOMEREA Network are listed in the **supplementary appendix** (Supplemental Digital Content 6, http://links.lww.com/CCM/E185).

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/ccmjournal).

The OUTCOMEREA research network entirely funded the study.

The authors have disclosed that they do not have any potential conflicts of interest.

For information regarding this article, E-mail: timsit@bch.aphp.fr

Objectives: To investigate the respective impact of ventilator-associated pneumonia and ICU–hospital-acquired pneumonia on the 30-day mortality of ICU patients.

Design: Longitudinal prospective studies.

Setting: French ICUs.

Patients: Patients at risk of ventilator-associated pneumonia and ICU–hospital-acquired pneumonia.

Interventions: The first three episodes of ventilator-associated pneumonia or ICU–hospital-acquired pneumonia were handled as time-dependent covariates in Cox models. We adjusted using the case-mix, illness severity, Simplified Acute Physiology Score II score at admission, and procedures and therapeutics used during the first 48 hours before the risk period. Baseline characteristics of patients with regard to the adequacy of antibiotic treatment were analyzed, as well as the Sequential Organ Failure Assessment score variation in the 2 days before the occurrence of ventilator-associated pneumonia or ICU–hospital-acquired pneumonia. Mortality was also analyzed for *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter species* (ESKAPE) and *P. aeruginosa* pathogens.

Copyright © 2018 by the Society of Critical Care Medicine and Wolters Kluwer Health, Inc. All Rights Reserved.

Measurements and Main Results: Of 14,212 patients who were admitted to the ICUs and who stayed for more than 48 hours, 7,735 were at risk of ventilator-associated pneumonia and 9,747 were at risk of ICU–hospital-acquired pneumonia. Ventilator-associated pneumonia and ICU–hospital-acquired pneumonia occurred in 1,161 at-risk patients (15%) and 176 at-risk patients (2%), respectively. When adjusted on prognostic variables, ventilator-associated pneumonia (hazard ratio, 1.38 (1.24–1.52); $p < 0.0001$) and even more ICU–hospital-acquired pneumonia (hazard ratio, 1.82 [1.35–2.45]; $p < 0.0001$) were associated with increased 30-day mortality. The early antibiotic therapy adequacy was not associated with an improved prognosis, particularly for ICU–hospital-acquired pneumonia. The impact was similar for ventilator-associated pneumonia and ICU–hospital-acquired pneumonia mortality due to *P. aeruginosa* and the ESKAPE group.
Conclusions: In a large cohort of patients, we found that both ICU–hospital-acquired pneumonia and ventilator-associated pneumonia were associated with an 82% and a 38% increase in the risk of 30-day mortality, respectively. This study emphasized the importance of preventing ICU–hospital-acquired pneumonia in nonventilated patients. (*Crit Care Med* 2019; 47:345–352)
Key Words: intensive care unit; intensive care unit–hospital-acquired pneumonia; mortality; ventilator-associated pneumonia

Nosocomial pneumonia is the most commonly reported infection in ICUs, with mechanically ventilated patients being at the highest risk. The prevalence of ventilator-associated pneumonia (VAP) ranges from 8% to 28% (1, 2). VAP is associated with significant increases in hospital stay length and morbidity (3). The excess risk of death attributable to VAP varies considerably across studies. In contrast to VAP, data on nosocomial pneumonia occurring in the ICU in patients without invasive mechanical ventilation (IMV) (ICU–hospital-acquired pneumonia [ICU-HAP]) are scarce (4). They only suggest that their crude hospital mortality estimates are similar to that of VAP. Indeed, similar analyses for ICU-HAP occurring in noninvasively ventilated ICU patients and using modern statistics for comparison to VAP have not yet been published.

An early implementation of an adequate treatment is undoubtedly a major prognostic factor for mortality (5). Guidelines from the American Thoracic Society suggest that patients with suspected HAP should be treated according to the results of microbiological testings performed on respiratory samples obtained noninvasively, rather than being treated empirically; the importance of deescalating the antibiotic therapy based upon respiratory and blood culture results was also reported (1).

The purpose of the present study was to compare the mortality associated with ICU-HAP and with VAP. We were also interested in the effect of early antibiotic therapy adequacy on VAP and ICU-HAP mortality. We analyzed data extracted from a large prospective multicenter high-quality French OUTCOMEREA database, and we used models that took into account competing risks.

MATERIALS AND METHODS

Study Design and Data Source

This observational study was conducted using a multicentre longitudinal database fuelled from 1997 by 23 ICUs contributing to the OUTCOMEREA network. The methodology implemented for data collection and quality control has been extensively described elsewhere (6). Briefly, patients more than 18 years old and with an ICU stay longer than 24 hours were randomly selected every year in each participating ICU. Data were collected at admission (demographical characteristics, chronic diseases, admission features, baseline severity indexes, admission diagnosis and admission type), then recorded on a daily basis throughout the ICU stay (daily assessment of organ functions, intensive care procedures, iatrogenic events, carriage of multidrug-resistant [MDR] pathogens, ICU-acquired infections, antibiotic exposure, length of stay, final diagnoses of the ICU stay, decision to withhold or withdraw life-sustaining therapies, and vital status at ICU and hospital discharge). These data were prospectively entered into the database through an anonymized electronic case report from using the Vigirea and Rhea software (OutcomeRea, Rosny-sous-Bois, France). The French Advisory Committee for Data Processing in Health Research, the French Informatics and Liberty Commission, and the Ethics Committee of Clermont-Ferrand University, France, approved this database collection.

Ethical Issues

This study was approved by our institutional review board, which waived the need for signed informed consent of the participants, in accordance with French legislation on noninterventional studies. However, the patients and their next of kin were informed of their inclusion into the database and could decline participation.

Definitions of Pneumonia, Microbiologic Processing, and Antimicrobial Treatment

IMV is defined as continuous ventilation via endotracheal tube or tracheotomy and noninvasive ventilation as positive pressure ventilation with different pressure levels via face mask or helmet performed intermittently or continuously. Patients were considered at risk of VAP after at least 2 days of IMV. Similarly, patients were considered at risk of ICU-HAP after at least 2 days of ICU stay without IMV. Patients considered for only one or both analyses were those. Patients with a new or persistent infiltrate on chest radiography that was associated with one of the following criteria: 1) purulent tracheal secretions, 2) fever greater than or equal to 38.5°C or hypothermia less than or equal to 36.5°C, and 3) leukocytosis greater than 10^9 G/L or leukopenia less than 4.10^8 G/L were suspected to have pulmonary infection. Microbiological samplings taken into account were bronchoalveolar lavage fluid (significant threshold, $\geq 10^4$ cfu/mL) or plugged telescopic catheter (significant threshold, $\geq 10^3$ cfu/mL) or quantitative endotracheal aspirate (significant threshold, $\geq 10^5$ cfu/mL), for both VAP and ICU-HAP. When bacteriological examinations yielded only coagulase-negative staphylococci or *Enterococcus* species,

Copyright © 2018 by the Society of Critical Care Medicine and Wolters Kluwer Health, Inc. All Rights Reserved.

nosocomial pneumonia diagnosis was accepted after check by a senior investigator. Only confirmed VAP cases were used to establish the model. When VAP was suspected, patients were sampled before any changes in antibiotic therapy.

Adequate antimicrobial treatment required a microbiologically documented infection (supported by positive culture results from an appropriate clinical specimen), received at least within the first 24 hours after VAP or ICU-HAP occurrence. High-risk pathogens were defined as MDR bacteria and clustered into four classes: methicillin-resistant *Staphylococcus aureus*, extended-spectrum β-lactamase–producing *Enterobacteriaceae*, AmpC-producing *Enterobacteriaceae*, and *Pseudomonas aeruginosa* resistant to ticarcillin and/or imipenem and/or ceftazidime. A patient was considered as colonized if one of these four microorganisms were isolated from screening sample (perirectal, nose, any screening sample). We assumed that colonized patients remained colonized during the full study period.

Data Collection

All relevant data from the medical records and bedside flow charts of patients more than 18 years old, including clinical, laboratory, radiology, and microbiology information, were collected at admission and during the ICU stay. Follow-up for each patient was extended to death or loss of patient follow-up.

Statistical Analyses

Characteristics of patients were described as count and percent or median and interquartile range for qualitative and quantitative variables, respectively, and were compared between groups using chi-square or Mann-Whitney *U* tests, as appropriate.

Patient at risk for ICU-HAP are different from those at risk for VAP. To identify death risk factors in patients at risk for VAP or ICU-HAP, we used two distinct univariate Cox models, both stratified by center. Variables identified as significantly associated with mortality by the univariate models were inserted into a multivariate model with a stepwise selection. The period at risk of VAP started after 2 days of IMV and after 2 days in ICU for ICU-HAP.

Data were processed similarly for ICU-HAP and VAP analyses. In cases of multiple episodes of pneumonia, the first three episodes of pneumonia were taken into account as time-dependent variables in the model. The model was adjusted on the risk factors of death and stratified by center. Patients were censored after 30 days. Patients discharged alive from the hospital to rehabilitation, a long-term setting, or home before 30 days were considered alive at day 30 ($n = 764$ and 1,611 for VAP and ICU-HAP risk groups, respectively). The functional form was checked with cumulative sums of martingale residuals and a proportional hazard model, with the observed scores processed against time.

The same analyses were performed, taking into account the adequacy of treatment at the 24 first hours after pneumonia diagnosis. Sensitivity analyses that excluded patients with therapeutic limitations were performed in both ICU-HAP and VAP risk groups. Baseline characteristics of patients with regard to the adequacy of antibiotic treatment were analyzed as well as the slope of the Sequential Organ Failure Assessment (SOFA) score in the 2 days before the occurrence. The ICU-HAP mortality was also analyzed for ESKAPE and *P. aeruginosa* pathogens.

p values lower than 0.05 were considered to be significant. Statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Epidemiology and Clinical Features

A flow diagram is presented in **Figure 1**. Of 14,212 patients who were admitted in the ICUs and who stayed for more than 48 hours, 7,735 were at risk of VAP and 9,747 were at risk of ICU-HAP. VAP and ICU-HAP occurred in 1,161 at-risk patients (8%) and 176 at-risk patients (1%), respectively. VAP and ICU-HAP occurred after a median delay at risk of 6 days (3–10 d) and 2 days (1–5 d), respectively (**Fig. 2**). Among ICU-HAP episodes, 32 (23.7%) required intubation within 48 hours after diagnosis.

Recurrent pneumonia was observed in 173 patients and nine patients in the VAP group and ICU-HAP group, respectively. There were 3,270 patients successively at risk for ICU-HAP and VAP. Of the 9,747 patients at risk for ICU-HAP, 6% developed VAP in days prior to their ICU stay.

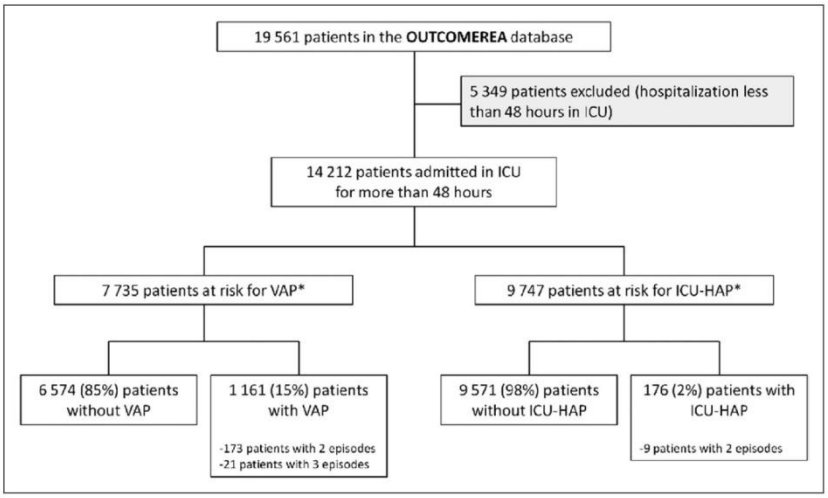


Figure 1. Population flowchart. ICU-HAP = ICU–hospital-acquired pneumonia, VAP = ventilator-associated pneumonia, OUTCOMEREA database = multicenter longitudinal database fueled by ICUs contributing to the OUTCOMEREA Network.

Copyright © 2018 by the Society of Critical Care Medicine and Wolters Kluwer Health, Inc. All Rights Reserved.

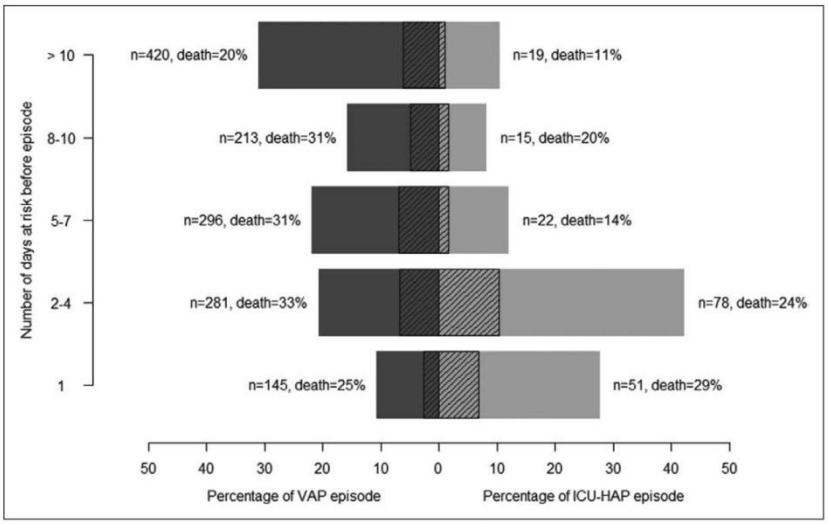


Figure 2. Time to occurrence of ICU–hospital-acquired pneumonia (ICU-HAP) and ventilator-associated pneumonia (VAP) episodes and associated mortality. The period at risk of VAP starts after 2 d of invasive mechanical ventilation. The period at risk of ICU-HAP starts after 2 d of ICU stay without invasive mechanical ventilation. Patients may have consecutively be exposed to both risks (patient B) and may be included in both analyses.

Baseline characteristics of both populations at risk and population with VAP/ICU-HAP are presented in **Table 1**. Among the 9,747 patients at risk for ICU-HAP, we register 179 cases of tracheobronchitis (1.8%) during the risk period: 161 (1.7%) in the patients without ICU- HAP and 18 (10.2%) in patients with ICU-HAP. The main microorganisms recovered were *S. aureus, P. aeruginosa*, and *Enterobacteriaceae* species, with a very similar distribution between ICU-HAP and VAP populations (**Table 2**). The rates of MDR organisms (*S. aureus*, *P. aeruginosa*, *Enterobacteriaceae* species) were not different between episodes of ICU-HAP and VAP.

The adequacy of initial treatment was 73% in patients with ICU-HAP episode and 69% in patients with VAP episodes.

Outcomes

VAP Mortality. The 30-day mortality rate after VAP onset was 330 (28.4%). **Supplemental Table 1** (Supplemental Digital Content 1, http://links.lww.com/CCM/E173) summarizes the mortality risk factors in the VAP group. A Cox model was performed that incorporated the first three VAP episodes as time-dependent variables and adjusted. This model identified VAP as an independent risk factor for mortality (hazard ratio [HR], 1.38 [1.24–1.52]). When the adequacy of treatment was taken into account, the mortality was not significantly higher in the inadequately treated arm (HR, 1.52 [1.27–1.82] vs HR, 1.31 [1.16–1.48]).

ICU-HAP Mortality. In the ICU-HAP risk group, 42 patients (23.9%) died within the 30 days of ICU-HAP onset after 9 days (4–16 d) in median. Causes of death were sorted out into four groups: considered by the investigator directly related to ICU-HAP in 15 patients, due to other causes in 17 patients, and to a therapeutic limitation in eight patients. Establishing the cause was unclear in two patients. Our results concluded that ICU-HAP 1.82 (1.35–2.45) is an independent risk factor for mortality (**Supplemental Table 2**, Supplemental Digital Content 2, http://links.lww.com/CCM/E174). Results remained similar when excluding ICU-HAP yielding only coagulase-negative staphylococci or *Enterococcus* species 1.88 (1.38–2.56). Of the 75 patients who were reintubated for ICU-HAP, 24 (32%) ultimately died within 30 days. The 30-day mortality of the remaining 101 patients was 18 (16%), *p* value equals to 0.012. NIV was associated with an increase in the risk of ICU-HAP. Paradoxically, when we performed sensitivity analyses comparing patients with and without NIV in the 2 days before ICU-HAP risk period, the increase in the risk of 30-day mortality due to ICU-HAP was higher in at-risk patients who did not receive NIV before the period at risk (adjusted HR, 2.019 [1.425–2.859] and 1.284 [0.715–2.303], respectively). Adequate therapy within the first 24 hours was not associated with an improvement in the prognosis of ICU-HAP (HR, 2.10 [1.51–2.92] vs HR, 1.19 [0.61–2.30]).

Characteristics of patients with ICU-HAP according to the adequacy of therapy are presented in **Supplemental Table 3** (Supplemental Digital Content 3, http://links.lww.com/CCM/E175). In the ICU-HAP patients, the modification of SOFA and the respiratory component of the SOFA score were not different according to the adequacy of the antibiotic therapy (Supplemental Table 3, Supplemental Digital Content 3, http://links.lww.com/CCM/E175). Adequate therapy was only associated with a trend of lower risk to be intubated within 48 hours of ICU-HAP (Supplemental Table 3, Supplemental Digital Content 3, http://links.lww.com/CCM/E175).

In our study, we did not observe a better outcome for patients with ICU-HAP according to the adequacy of empirical therapy. The characteristics of patients with adequate versus inadequate treatment were well balanced. The effect was similar according to the level of severity at ICU admission and the beginning of the risk period and according to the identified microorganisms (*P. aeruginosa*, ESKAPE group) (**Supplemental Table 4**, Supplemental Digital Content 4, http://links.lww.com/CCM/E176).

Similar subgroup analyses were performed for VAP (**Supplemental Table 5**, Supplemental Digital Content 5, http://links.lww.com/CCM/E177). The impact of VAP was similar for VAP due to *P. aeruginosa*, microorganisms of the

Copyright © 2018 by the Society of Critical Care Medicine and Wolters Kluwer Health, Inc. All Rights Reserved.

TABLE 1. Baseline Characteristics and Mortality Rate for Patients With Ventilator-Associated Pneumonia and ICU–Hospital-Acquired Pneumonia

Characteristics	Patients at Risk for VAP		Patients at Risk for ICU-HAP	
	No VAP ($n = 6574$)	VAP ($n = 1161$)	No ICU-HAP ($n = 9571$)	ICU-HAP ($n = 176$)
Male gender, *n* (%)	4,033 (61.3)	810 (69.8)	5,870 (61.3)	146 (83)
Age, median (quartile 1, quartile 3)	66 (51, 75)	66 (54, 75)	63 (51, 75)	69 (54, 78)
Simplified Acute Physiology Score II, median (quartile 1, quartile 3)	50 (38, 63)	49 (38, 62)	37 (27, 49)	41.5 (33, 52)
Comorbidities, *n* (%)				
Chronic hepatic failure	472 (7.2)	78 (6.7)	630 (6.6)	11 (6.3)
Chronic heart failure	948 (14.4)	167 (14.4)	1,523 (15.9)	31 (17.6)
Chronic respiratory failure	1,025 (15.6)	231 (19.9)	1,688 (17.6)	35 (19.9)
Chronic renal failure	328 (5)	57 (4.9)	671 (7)	8 (4.5)
Immunodeficiency	1,047 (15.9)	186 (16)	1,868 (19.5)	35 (19.9)
Admission category (missing $n = 20$ and 35) , *n* (%)				
Medical	4,710 (71.8)	892 (77)	7,334 (76.9)	126 (71.6)
Emergency surgery	1,273 (19.4)	163 (14.1)	1,327 (13.9)	30 (17)
Scheduled surgery	573 (8.7)	104 (9)	875 (9.2)	20 (11.4)
Diagnosis at the ICU admission (missing $n = 58$ and 91), *n* (%)				
Shock/multiple organ failure	1,992 (30.5)	303 (26.3)	2,014 (21.2)	30 (17)
Respiratory distress/chronic obstructive pulmonary disease exacerbation	1,957 (30)	474 (41.2)	3,235 (34.1)	82 (46)
Renal failure, *n* (%)	138 (2.1)	24 (2.1)	692 (7.3)	8 (4.5)
Coma	1,626 (24.9)	243 (21.1)	897 (9.5)	20 (10.8)
Trauma /planned surgery	814 (12.5)	106 (9.2)	2,642 (27.9)	38 (21.6)
VAP/HAP occurrences (days at risk)[a]				
First episode, median [quartile 1—quartile 3]	–	6 [3–10]	–	2 [1–5]
Second episode, median [quartile 1—quartile 3]	–	14 [10–19]	–	9 [8–17]
Third episode, median [quartile 1—quartile 3]	–	19 [12–24]	–	–
ICU length of stay (d), median [quartile 1—quartile 3]	6 [3–13]	21 [13–35]	3 [1–5]	13.5 [6–28]
ICU mortality rate, *n* (%)	1,700 (25.9)	377 (32.5)	649 (6.8)	45 (25.6)
Hospital length of stay (d), median [quartile 1—quartile 3]	16 [7–32]	32 [19–54]	15 [8–27]	26 [14–52]
Hospital mortality rate, *n* (%)	2,295 (34.9)	494 (42.5)	1,415 (14.8)	63 (35.8)

ICU-HAP = ICU–hospital-acquired pneumonia, VAP = ventilator-associated pneumonia.

[a]The period at risk of VAP starts after 2 d of invasive mechanical ventilation. The period at risk of ICU-HAP starts after 2 d of ICU stay without invasive mechanical ventilation.

ESKAPE group, and other microorganisms. The HR of the day-30 mortality associated with VAP was more pronounced in patients with a lower Simplified Acute Physiology Score (SAPS) II score at admission and lower SOFA score at the beginning of the at-risk period (Supplemental Table 5, Supplemental Digital Content 5, http://links.lww.com/CCM/E177). The rate of therapeutic limitations decision was similar between ICU-HAP and VAP decedents, 12 of 42 (29%) and 134 of 538 (25%), respectively. The results were not different when patients with therapeutic limitations were excluded (HR, 1.691 [1.23–2.32] for ICU-HAP and 1.38 [1.24–1.53] for VAP).

DISCUSSION

This is the largest study comparing mortality risk associated with VAP and with ICU-HAP. Both VAP and, to a greater

Copyright © 2018 by the Society of Critical Care Medicine and Wolters Kluwer Health, Inc. All Rights Reserved.

TABLE 2. Main Microorganisms Causing Ventilator-Associated Pneumonia and ICU–Hospital-Acquired Pneumonia Episode

Microorganisms, n (%)	Ventilator-Associated Pneumonia (*n* = 1,355)	ICU–Hospital-Acquired Pneumonia (*n* = 185)
Gram positive		
Streptococcus pneumoniae	66 (4.9)	5 (2.7)
Other Streptococci	61 (4.5)	7 (3.8)
Staphylococcus aureus	258 (19)	34 (18)
Methicillin susceptible	158 (11.7)	23 (12.4)
Methicillin resistant	100 (7.4)	11 (5.6)
Enterococcus	25 (1.8)	5 (2.7)
S. epidermidis	58(4.3)	21 (11.1)
Other Gram-positive microorganisms	11 (0.8)	3 (1.6)
Gram negative		
Enterobacteriaceae	438 (32.3)	51 (27.6)
Susceptible to third generation cephalosporin	340 (25.1)	39 (21.1)
Resistant to third generation cephalosporin	98 (7.2)	12 (6.5)
Pseudomonas aeruginosa	454 (33.5)	62 (33.5)
Susceptible	312 (23)	29 (15.7)
Resistant to ticarcillin, ceftazidime or penems	142 (10.5)	33 (17.8)
Stenotrophomonas maltophilia	64 (4.7)	4 (2.2)
Other *Pseudomonas* species	10 (0.7)	2 (1.1)
Other Gram-negative bacilli	118 (8.7)	22 (11.6)
Acinetobacter baumannii	48 (3.5)	4 (2.1)
Legionella pneumophila	2 (0.1)	2 (1.1)
Other Gram-negative microorganisms	15 (1.1)	4 (2.1)
Others		
Anaerobes	7 (0.5)	
Actinomycetes	1 (0.1)	
Intracellular bacteria		1 (0.5)
More than one microorganism	308 (22.7)	43 (23.2)

Other Gram-positive bacilli: *Bacillus* species, *B. cereus*, *Corynebacterium* species, *Lactobacillus* species, *Rhodococcus equi*; other Gram-negative cocci: *Moraxella catarrhalis*, *Moraxella* species, *Neisseria* species; other *Pseudomonas* species: *P.* fluoescens, *P.* putida, *P.* stuzeri, other species of *Pseudomonas*; other Gram-negative bacilli: *Rochalimeae* species, *Bartonella quintana*, *B. hensalae*, other species of *Bartonella*, *Helicobacter pylori*, *Campylobacter* species, *Helicobacter jejuni*, *Haemophilus influenzae*, other species of *Haemophilus*, *Vibrionaceae* species, *Brucella* species.

extent, ICU-HAP are independent risk factors for the 30-day mortality, even after adjustment for the case-mix.

Nonventilated HAP is underappreciated, although serious patient safety issue, resulting in significant increases in cost, length of stay, and mortality (7). Indeed, nonventilated HAP represented about two thirds of cases of nosocomial pneumonia diagnosed, and they were associated with a heavy overall economic burden. Their prevalence was 1.22–8.9 per 1,000 patient-days, and their mortality ranged from 13.1% to 19% (7–9).

The mortality of VAP in ICU has been extensively studied, whereas the impact of HAP in noninvasively ventilated or nonventilated ICU patients has been incompletely addressed. Indeed, its evaluation is hampered by the lack of systematic bacteriological samples and the uncertainties about bacteriological etiologies in about half of ICU-HAP cases (4, 10). The 23% crude mortality rate that we observed in ICU-HAP patients was rather similar to rates observed in previous studies in ICUs (4, 10) and often higher than the rates associated with nonventilated HAP observed in the wards (7–9, 11).

Copyright © 2018 by the Society of Critical Care Medicine and Wolters Kluwer Health, Inc. All Rights Reserved.

Studies evaluating the excess risk of death of nonventilated HAP patients are scarce. In an exposed-unexposed study, nonventilated patients with clinically diagnosed HAP and occurring in the ward were compared with a nonventilated control population; the odds ratio of death was 8.4 times higher in patients with HAP (11). In patients who received noninvasive ventilation, the occurrence of nosocomial pneumonia was also associated with an increase in the risk of intubation and death in two monocentric studies (12, 13).

Very few studies that have focused on ICU patients have compared the attributable mortality of ICU-HAP and VAP. In the KISS (German nosocomial infection surveillance system) registry, the crude mortality of patients who develop pneumonia under noninvasive ventilation was similar to that observed with VAP (10). Hospital mortality rates for patients with ICU-HAP were 36% in the study from Esperatti et al (4), with no difference in VAP mortality (42%) during the same period. In postoperative pneumonia, mortality due to VAP tended to be higher than that of ICU-HAP (24% vs 18%; $p = 0.09$) (14). One retrospective single-center trial suggests that the crude mortality of ICU-HAP patients with *Acinetobacter baumannii* was higher than that associated with VAP due to the same microorganism (15). Discrepancies between these results were probably related to the severity of ICU-HAP episodes. Indeed, the crude hospital mortality of ICU-HAP ranged from 22% when invasive ventilation was not required up to 48% when patients required mechanical ventilation (4).

The impact of adequate therapy on survival was minor in our VAP patients, fueling the current debate on its importance. A meta-analysis showed a significant increase in the risk of death associated with inadequate therapy. However, the impact is probably overestimated because of significant publication bias and a substantial heterogeneity of the results (16). One major reason for the discrepancies between estimations is the magnitude of the attributable mortality in VAP. It has repeatedly been demonstrated that the impact on mortality is highly dependent on the severity of patients' illness severity (5, 17–19). The impact is almost negligible or very limited for very critically ill patients with high severity (SAPS II or Acute Physiology and Chronic Health Evaluation II) or organ dysfunction scores (SOFA) at ICU admission. Importantly, most of our knowledge about the risk factors and the prognostic impact of inadequate initial antimicrobial treatment is based on studies on VAP, as most well-conducted studies focused on such patients populations (5, 17–21).

Our study has several strengths. It is the largest study published in the field. We used a high-quality database, the diagnosis of pneumonia was based on strong bacteriological criteria, and all bacteriological results were checked before analyses. Most of the patients were followed for up to 30 days, making bias due to informative censor improbable. We carefully adjusted on the analyses on prognostic factors available at the beginning of the at-risk period. Furthermore, more than one episode of pneumonia was taken into account in analyzing the impact of pneumonia on mortality, which increased the study power.

This study also has some limitations. We were unable to detect a positive impact of adequate therapy for ICU-HAP patients in the full-set analysis and in various sensitivity analyses that accounted for disease severity so recovered bacteria. The rate of intubation within 48 hours of ICU-HAP was higher, although not significant, in the case of inadequate therapy, but the inadequacy of therapy did not influence the improvement of organ dysfunctions. Many factors could explain this negative result, starting with the small sample size and an insufficient power that is the most likely. Indeed, only 185 cases of ICU-HAP were observed, and only 27 % of them were inadequately treated. Second, we selected only microbiologically confirmed ICU-HAP. Using an insufficiently accurate ICU-HAP definition may lead to overtreat some patients, with potentially harmful effects. However, we used strict definitions that required either a positive quantitative culture or a positive test for *Legionella* species Third, our prevalence of pathogenic distribution may not be generalizable to all institutions. Adequate early bacterial killing is not always associated with an improvement of the inflammatory process involved in ICU-HAP. In other words, when the treatment is introduced too late because of late diagnosis, it might be unable to reverse the disease course (22). Fourth, viral coinfections, are detectable in one fourth of the cases and have been shown recently to aggravate the prognosis of pneumonia (23, 24). Research of viral coinfections was not performed routinely in the database and may also explain our results. Finally, all-cause mortality may be related to underlying comorbidities that influence the relationship between the adequacy of antimicrobial treatment and death.

CONCLUSIONS

ICU-HAP was associated with an 82% increase in the risk of death at day 30. This effect was significant and even higher than the one observed with VAP. In our large, prospectively collected database, the impact of the adequacy of empirical therapy was limited for VAP and not observed for ICU-HAP.

ACKNOWLEDGMENTS

We are thankful to Céline Féger, MD (EMIBiotech), for her editorial support.

REFERENCES

1. Kalil AC, Metersky ML, Klompas M, et al: Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infect Dis* 2016; 63:e61–e111
2. Torres A, Niederman MS, Chastre J, et al: International ERS/ESICM/ESCMID/ALAT guidelines for the management of hospital-acquired pneumonia and ventilator-associated pneumonia: Guidelines for the management of hospital-acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP) of the European Respiratory Society (ERS), European Society of Intensive Care Medicine (ESICM), European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and Asociacion Latinoamericana del Torax (ALAT). *Eur Respir J* 2017; 50:1700582
3. Safdar N, Dezfulian C, Collard HR, et al: Clinical and economic consequences of ventilator-associated pneumonia: A systematic review. *Crit Care Med* 2005; 33:2184–2193

Copyright © 2018 by the Society of Critical Care Medicine and Wolters Kluwer Health, Inc. All Rights Reserved.

4. Esperatti M, Ferrer M, Theessen A, et al: Nosocomial pneumonia in the intensive care unit acquired by mechanically ventilated versus nonventilated patients. *Am J Respir Crit Care Med* 2010; 182:1533–1539
5. Clec'h C, Timsit JF, De Lassence A, et al: Efficacy of adequate early antibiotic therapy in ventilator-associated pneumonia: Influence of disease severity. *Intensive Care Med* 2004; 30:1327–1333
6. Reignier J, Darmon M, Sonneville R, et al; OutcomeRea Network: Impact of early nutrition and feeding route on outcomes of mechanically ventilated patients with shock: A post hoc marginal structural model study. *Intensive Care Med* 2015; 41:875–886
7. Giuliano KK, Baker D, Quinn B: The epidemiology of nonventilator hospital-acquired pneumonia in the United States. *Am J Infect Control* 2018; 46:322–327
8. Magill SS, Edwards JR, Bamberg W, et al; Emerging Infections Program Healthcare-Associated Infections and Antimicrobial Use Prevalence Survey Team: Multistate point-prevalence survey of health care-associated infections. *N Engl J Med* 2014; 370: 1198–1208
9. Sopena N, Sabrià M; Neunos 2000 Study Group: Multicenter study of hospital-acquired pneumonia in non-ICU patients. *Chest* 2005; 127:213–219
10. Kohlenberg A, Schwab F, Behnke M, et al: Pneumonia associated with invasive and noninvasive ventilation: An analysis of the German nosocomial infection surveillance system database. *Intensive Care Med* 2010; 36:971–978
11. Micek ST, Chew B, Hampton N, et al: A case-control study assessing the impact of nonventilated hospital-acquired pneumonia on patient outcomes. *Chest* 2016; 150:1008–1014
12. Zhang Z, Duan J: Nosocomial pneumonia in non-invasive ventilation patients: Incidence, characteristics, and outcomes. *J Hosp Infect* 2015; 91:153–157
13. Girou E, Schortgen F, Delclaux C, et al: Association of noninvasive ventilation with nosocomial infections and survival in critically ill patients. *JAMA* 2000; 284:2361–2367
14. Dupont H, Montravers P, Gauzit R, et al; Club d'Infectiologie en Anesthésie-Réanimation: Outcome of postoperative pneumonia in the Eole study. *Intensive Care Med* 2003; 29:179–188
15. Yang YS, Lee YT, Huang TW, et al: Acinetobacter baumannii nosocomial pneumonia: Is the outcome more favorable in non-ventilated than ventilated patients? *BMC Infect Dis* 2013; 13:142
16. Paul M, Shani V, Muchtar E, et al: Systematic review and meta-analysis of the efficacy of appropriate empiric antibiotic therapy for sepsis. *Antimicrob Agents Chemother* 2010; 54:4851–4863
17. Bekaert M, Timsit JF, Vansteelandt S, et al; Outcomerea Study Group: Attributable mortality of ventilator-associated pneumonia: A reappraisal using causal analysis. *Am J Respir Crit Care Med* 2011; 184:1133–1139
18. Melsen WG, Rovers MM, Groenwold RH, et al: Attributable mortality of ventilator-associated pneumonia: A meta-analysis of individual patient data from randomised prevention studies. *Lancet Infect Dis* 2013; 13:665–671
19. Nguile-Makao M, Zahar JR, Français A, et al: Attributable mortality of ventilator-associated pneumonia: Respective impact of main characteristics at ICU admission and VAP onset using conditional logistic regression and multi-state models. *Intensive Care Med* 2010; 36:781–789
20. Timsit JF, Zahar JR, Chevret S: Attributable mortality of ventilator-associated pneumonia. *Curr Opin Crit Care* 2011; 17:464–471
21. Vallés J, Pobo A, García-Esquirol O, et al: Excess ICU mortality attributable to ventilator-associated pneumonia: The role of early vs late onset. *Intensive Care Med* 2007; 33:1363–1368
22. Rhodes A, Evans LE, Alhazzani W, et al: Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. *Intensive Care Med* 2017; 43:304–377
23. Loubet P, Voiriot G, Houhou-Fidouh N, et al: Impact of respiratory viruses in hospital-acquired pneumonia in the intensive care unit: A single-center retrospective study. *J Clin Virol* 2017; 91:52–57
24. Voiriot G, Visseaux B, Cohen J, et al: Viral-bacterial coinfection affects the presentation and alters the prognosis of severe community-acquired pneumonia. *Crit Care* 2016; 20:375

Copyright © 2018 by the Society of Critical Care Medicine and Wolters Kluwer Health, Inc. All Rights Reserved.

3) Article 4 (publié, Critical care medecine)

Weiss *et al. Critical Care* (2017) 21:162
DOI 10.1186/s13054-017-1755-5

Critical Care

RESEARCH Open Access

Treatment of severe hospital-acquired and ventilator-associated pneumonia: a systematic review of inclusion and judgment criteria used in randomized controlled trials

Emmanuel Weiss[1,2,3*], Wafa Essaied[4], Christophe Adrie[5], Jean-Ralph Zahar[4,6] and Jean-François Timsit[2,4,7]

Abstract

Background: Hospital-acquired and ventilator-associated pneumonia (HAP/VAP) are often selected for randomized clinical trials (RCTs) aiming at new drug approval. Guidelines for the design of such RCTs have been repeatedly updated by regulatory agencies. We hypothesized that large variability in the enrolled populations, the endpoints assessed and the HAP/VAP definition criteria may impact the results of these studies, and addressed this through a systematic review of HAP/VAP RCTs.

Methods: A search (Pubmed-Embase-ICAAC-ECCMID) of all RCTs published between 1994 and 2016 comparing antimicrobial treatment for HAP/VAP in the intensive care unit was conducted. The populations enrolled, inclusion/exclusion criteria, statistical design and endpoints assessed were recorded. All unpublished RCTs recorded on the ClinicalTrials.gov registry were also screened.

Results: From the 93 abstracts reviewed, 39 potentially relevant studies were inspected, leading to 27 studies being included. As expected, illness severity or the proportion with VAP (27–100%) differed greatly among the enrolled populations. The HAP/VAP definition used various clinical and biological criteria, and only 55% of studies required a microbiological sample. The mandatory duration of prior hospital stay was variable; the mechanical ventilation duration was an inclusion criterion in only 41% of VAP studies. Nine studies had non-inferiority design, but nine studies (33%) did not have a pre-specified statistical hypothesis. Clinical cure was the primary endpoint in 24 studies, but was recorded in several populations or as the co-primary endpoint in 13 studies. The definition of clinical cure and the timing of its assessment greatly differed. This variability slightly improved over time but remained significant in the 13 registered but currently unpublished RCTs that we screened.

Conclusion: Our study provides a description of populations and endpoints of RCTs evaluating antimicrobials for treatment of HAP/VAP in the ICU. There was significant heterogeneity in enrollment criteria, endpoints and statistical design, which may influence the ability of studies to demonstrate differences between studied drugs.

Keywords: Systematic review, Hospital-acquired pneumonia treatment, Ventilator-acquired pneumonia treatment, Randomized controlled trials, Endpoints, Inclusion criteria

* Correspondence: emmanuel.weiss@aphp.fr
[1]Department of Anesthesiology and Critical Care, HUPNVS, Hôpital Beaujon, APHP, 92110 Clichy, France
[2]Paris Diderot University, Paris, France
Full list of author information is available at the end of the article

BioMed Central

© The Author(s). 2017 **Open Access** This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.

Background

New antimicrobials are required to face the dramatically increasing prevalence of multidrug-resistant pathogens. This unmet need has become a worldwide source of concern, and government action plans aiming at increasing the antimicrobials pipeline are in development [1]. The evaluation of these new treatments will require properly designed studies with appropriate inclusion criteria and endpoints. However, in hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP), the way to conduct such studies remains unclear. During the past ten years, the regulatory agencies (European Medicines Agency (EMA) and Food and Drug Administration (FDA)) have repeatedly updated their guidelines for the design of randomized controlled trials (RCTs), but their recommendations remain conflicting, especially regarding the design, endpoints, or inclusion criteria that should be used [2, 3].

This is an important issue because HAP and VAP are ideal syndromes for clinical trials in the context of new drug approval: they are a major cause of infection, often involving multidrug-resistant pathogens (25% of ICU infections), they account for up to 50% of antibiotic prescriptions [4], identification of the causative pathogen using microbiological samples is easy, and they are particularly sensitive to antimicrobial treatment effect [5, 6].

Our hypothesis is that to date, HAP/VAP RCTs greatly differ in the population enrolled, the criteria used for definition of HAP/VAP, and the endpoints assessed. Such differences among studies may be of importance as they may impact the results of the studies. For example, some studies showed that the reported incidence of VAP greatly depends on the diagnostic methodology used. This systematic review describes the enrolled populations, design, and conduct of RCTs addressing the efficacy of antimicrobials for HAP/VAP treatment in intensive care unit (ICU) patients from 1994 to 2016.

Methods

The methodology of the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) guidelines was used for the conduct of the systematic review [7].

Search Strategy

We searched PubMed, Embase, ICAAC and ECCMID for publications from 1994 to 2016. The search string used was:

1-(Pneumonia and (hospitalized or acquired or ventilatory-associated or nosocomial or health-associated)) and (antibiotic treatment or (antibiotic therapy) or antibiotic or (antibacterial agents) or (anti-infective agents) or antimicrobial)

It was complemented by:

2-Pneumonia and (hospitalized or acquired or ventilatory-associated or nosocomial or health-associated)) and (doripenem or meropenem or impenem or linezolid or vancomycin or piperacillin or (piperacillin and tazobactam) or ceftazidim or ceftriaxone or cefotaxime or ceftobiprole or ciprofloxacin or levofloxacin or moxifloxacin or piperacillin or teicoplanin or cefepime or ticarcillin or (ticarcillin and clavulanic acid) or amikacin or tobramycin or gentamicin) and (randomized controlled trial).

Of note, some studies were identified through sources other than a database search, including contact with researchers.

Study selection

All RCTs evaluating the efficacy of antimicrobials in HAP/VAP in adult patients in the ICU from 1994 to 2016 were considered as eligible for this systematic review. The study selection process is detailed in a flow diagram (Fig. 1). The search period was limited to twenty years because of the evolution of publication requirements and treatment concepts. All articles were independently screened by two authors (J-RZ and CA). Full texts (and clinical trial registry data (ClinicalTrials.gov website)) of all potentially relevant studies were analyzed to assess eligibility. Disagreements on the inclusion/exclusion of studies were resolved in consultation with other co-authors (EW and J-FT). We included studies comparing one antibiotic agent to another, monotherapy to combination therapy, inhaled to systemic route or extended/continuous infusion to intermittent administration. Finally, in January 2017 we also searched the ClinicalTrials.gov website for characteristics of currently unpublished RCTs comparing HAP/VAP antimicrobial treatment strategies.

Recorded data

The following data were collected for each study included: inclusion and exclusion criteria, design, primary endpoint and population in which it was analyzed, definition of clinical cure, time point used for the test of cure (TOC) visit, and the statistical hypothesis. Data extraction from the studies was confirmed by an independent reviewer. At the end, a global quality assessment of each RCT was performed using an 8-item scale allowing calculation of a global quality score adapted to the focus of this systematic review.

Results

Populations enrolled

The main characteristics of the 27 studies included in the systematic review (see Additional file 1 for references) and of their enrolled populations are described in Table 1.

The number of patients enrolled in the intention-to-treat (ITT) population was highly variable and ranged from 35 to 945. Patients were predominantly male and

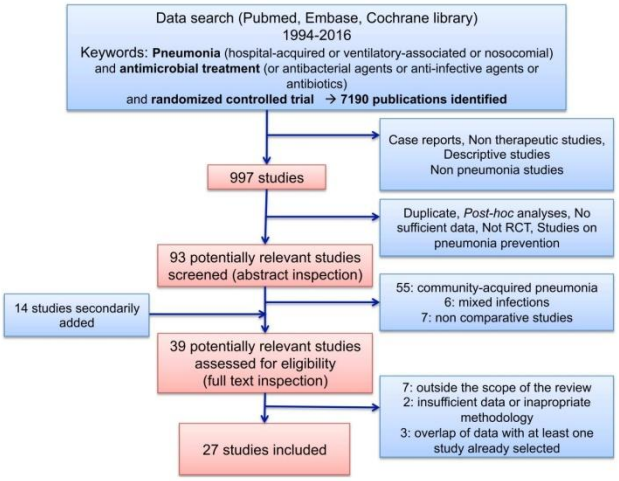


Fig. 1 Study selection flow diagram

the mean age across trials was 50.5–70.0 years. In most studies (92%), severity of illness was reported using the APACHE II score and its mean value varied from 13.8 to 24.0 across trials. The rate of comorbidity was rarely reported.

Sixteen studies co-enrolled patients with HAP and VAP and 11 studies exclusively enrolled patients with VAP. Among the former, the proportion of patients with VAP greatly varied from 27 to 91%. In some studies, randomization was stratified by patients' severity of illness (three trials) and on the rate of VAP (two trials). Whereas 18 studies (67%) included all HAP/VAP episodes regardless of the causative pathogen, some only enrolled patients with HAP/VAP related to specific pathogens. The duration of hospital stay before the onset of pneumonia was required to be longer than 48 hours and 72 hours in 18 studies (67%) and 7 studies (26%), respectively (not mentioned in the remaining study). However, the duration of the mechanical ventilation was an inclusion criterion in only 11 VAP studies (41%).

The diagnosis of pneumonia was consistently based on clinical and radiological (new lung infiltrate on chest radiography) findings but microbiological confirmation was required in only 15 studies (55%). Among the remaining studies, the proportion of patients analyzed who had positive respiratory samples varied from 62 to 82%. Clinical signs leading to suspicion of HAP/VAP were highly variable across the 27 studies. These clinical findings and the percentage of studies using them as inclusion criteria are shown in Fig. 2a. In 73% of studies, a predefined number of respiratory symptoms and signs of sepsis were required for pneumonia diagnosis and subsequent inclusion (Fig. 2b).

Various exclusion criteria were also reviewed. In five studies (20%), patients with severe disease, as reflected by high Acute Physiology and Chronic Health Evaluation (APACHE) score (four studies) or Simplified Acute Physiology Score (SAPS) (one study), concomitant septic shock (two studies) or acute respiratory distress syndrome (one study) were excluded. Neutropenia and immunosuppression (various definitions) were considered as exclusion criteria in 13 studies (48%) and 7 studies (26%), respectively. Finally, patients with chronic respiratory diseases were excluded in nine studies (33%).

Only a few studies tried to balance heterogeneity by stratifying the randomization according to the severity of the acute disease (APACHE in two studies and partial arterial oxygen pressure/fraction of inspired oxygen (PaO2/FiO2) ratio in one study) or the characteristics of the pneumonia (i.e., HAP or VAP, in three studies).

Clinical trial design

There were 21 multicenter studies (78%), 14 double-blinded studies (52%) and 13 open-labeled studies (48%). The duration of study therapy varied from one study to another (from 5 to 21 days) and was left at the discretion of the investigators in 37% of studies.

Nine trials (33%) used a non-inferiority design with non-inferiority margins (i.e., absolute percentage difference in the primary outcome acceptable for non-inferiority to be established) mentioned in eight of them (20%, 15% and 10% in three studies, four studies, and one study, respectively), but the scientific evidence leading to calculation of the non-inferiority margin was missing in two of them. Six studies (22%) and three studies (11%) were equivalence

Table 1 Selected characteristics of studies included in the systematic review

First author	Year of publication	Tested molecule	Comparator	Statistical design	Blinded	Causative pathogen	Patients with VAP (ITT or mITT, %)	Number of ITT patients	Patient with positive respiratory samples (% of ITT/primary endpoint population)	Mean age ± SD[a]	Mean Apache II score ± SD[a]	Duration of study therapy, (days)	Cure rate (%)	Mortality rate (%)
Jaccard	1998	Piperacillin/ tazobactam	Imipenem/ cilastatin	NM	Yes	All pathogens	NM	154	81/81	59.7 ± 16.9	14.9 ± 6.8	7–14	77	8.4[l]
Brun-Buisson	1998	Piperacillin/ tazobactam + amikacin	Ceftazidim + amikacin	Equivalence	No	All pathogens	100	204	62/100	55.5 ± 16	37.4 ± 1.4[f]	15–21	42	20[j]
Fagon	2000	Quinupristin/ dalfopristin	Vancomycin	Equivalence	No	Only Gram-positive pathogens	70	304	73/100	57 ± 18	15 ± 6.9	5–14	44	23[k]
Torres	2000	Ciprofloxacin	Imipenem/ cilastatin	NM	No	All pathogens	NM	149	68/100	61 ± 16	13.8 ± 8	NM	68	16[k]
Alvarez-Lerma	2001	Piperacillin/ tazobactam + amikacin	Ceftazidim + amikacin	Equivalence	No	All pathogens	85	124	56/64	59 ± 19	16.7 ± 6.5	NM	48	35[k]
Nicolau	2001	Continuous ceftazidime	Intermittent ceftazidime	NM	No	All pathogens	91	35	68/80	51 ± 18	14.5 ± 5.5	NM	37	NM
Rubinstein	2001	Linezolid	Vancomycin	Equivalence	Yes	All pathogens	63	396	42//NM	62 ± 18	15.5 ± 6.8	7	52	21[k]
Wunderlink	2003	Linezolid	Vancomycin	Equivalence	Yes	All pathogens	35	623	71//100	62.5 ± 19.1	14.1 ± 6	7–21	53	20[j]
Zanetti	2003	Cefepim	Imipenem/ cilastatin	Non inferiority	Yes	All pathogens	NM	209	NM/71	54 ± 18	15 ± 6.5	NM	39	22[i]
Shorr	2005	Levofloxacin	Imipenem/ cilastatin	Non inferiority	No	All pathogens	100	222	>50/>50	53 ± 21	15 ± 14	NM	61 [g]	NM
Joshi	2006	Piperacillin/ tazobactam + tobramycin	Imipenem/ cilastatin + tobramycin	Equivalence	Yes	All pathogens	69	437	92//100	52.3 ± 20	13.5	>5	53	NM
Schmidt	2006	Piperacillin/ tazobactam	Imipenem/ cilastatin	NM	Yes	All pathogens	NM	221	100/100	67 ± 13.7	13.4 ± 4.2	5–21	68 [g]	13[k]
Betrosian	2008	Ampicillin-sulbactam	Colistin	NM	No	*Acinetobacter baumanii*	100	28	100/100	70 ± 7	14 ± 3.5	8–10	68	28[h]
Chastre	2008	Doripenem	Imipenem/ cilastatin	Non inferiority	No	All pathogens	100	531	78/82	50,5 ± 19	RS 59 < 15	7–14	58	10[h]
Giamarallos-Bourboulls	2008	ATB + clarithromycin	ATB + placebo	NM	yes	All pathogens	100	200	100/100	58.4 ± 18.4	17 ± 6	NM	75	25[i]
Heyland	2008	Meropenem + ciprofloxacin	Meropenem	Superiority	no	All pathogens	100	740	82/82	59 ± 17.8	20 ± 6.3	NM	NM	19[h]
Freire	2010	Tigecyclin	Imipenem/ cilastatin	Non inferiority	yes	All pathogens	26.8	945	65/62	57.4 ± 18.6	RS 396 > 15	7–14	52	13[k]

Table 1 Selected characteristics of studies included in the systematic review *(Continued)*

Jung	2010	Vancomycin + rifampicin	Vancomycin	Superiority	no	Methicillin-resistant *Staphylococcus aureus*	73	83	100/100	69 (28-98)[b]	24 (15–38)[b]	14	42	30[h]
Rattanaum-pawan	2010	ATB + nebulized colistimetate	ATB + placebo	Superiority	no	Only Gram-negative pathogens	100	102	100/100	68 ± 16.5	18.7 ± 5	NS	52	42[h]
Lu	2011	Nebulized ceftazidime + amikacin	IV ceftazidim + amikacin	NM	No	*Pseudomonas aeruginosa*	100	40	100/100	59 ± 16	33 ± 13[f]	8	72	18[h]
Rubinstein	2011	Telavancin	Vancomycin	Non inferiority	Yes	Only Gram-positive pathogens	28	1503	60/73	62 ± 18	15.5 ± 6.2	7–21	59	19[h]
Aydemir	2012	Colistin	Colistin + rifampicin	NM	No	*Acinetobacter baumanii*	100	43	100/100	61 ± 20	19.1 ± 6	NS	46	67[k]
Kollef	2012	Doripenem	Imipenem	Non inferiority	Yes	All pathogens	100	227	74/100	54.7 ± 17.6	RS[e]	7–10	52	18[h]
Wunderlink	2012	Linezolid	Vancomycin	Non inferiority	Yes	*Staphylococcus aureus*	63	448	100/100	61 ± 18	17 ± 6	7–14	50	16[j]
Ramirez	2013	Tigecyclin Low dose/ Tigecyclin High dose	Imipenem/ cilastatin	Non inferiority	Yes	All pathogens	39	105	63/71	62 ± 15	13.8	NS	59	16[k]
Awad	2014	Ceftobiprol medocaril	Ceftazidim + vancomycin	Non inferiority	Yes	All pathogens	27	781	69/NM	RS[c]	RS[d]	7–14	51	17[i]
Kollef	2016	Imipenem or meropenem + Nebulized amikacin and fosfomycin	Imipenem or meropenem + placebo	NM	Yes	Only Gram-negative pathogens	100	143	100/100	62 ± 11	18.4 ± 5.9	10	23	20

APACHE Acute Physiology and Chronic Health Evaluation, *ITT* intention-to-treat, *mITT* microbiological ITT, *NM* not mentioned, *RS* reported by stratum only, *SAPS* Simplified Acute Physiology Score, *SD* standard deviation, *VAP* ventilator-associated pneumonia

[a]As provided in reports
[b]Median (range)
[c]362 patients were >65 years old
[d]205 patients had an APACHE II score >15
[e]128 patients had an APACHE II score >15
[f]Mean ± SD SAPS
[g]Clinical success rate (include clinical cure and clinical improvement)
[h]Day-28 mortality
[i]Day-30 mortality
[j]Day-60 mortality
[k]Mortality at the end of the study
[l]Infection-related mortality

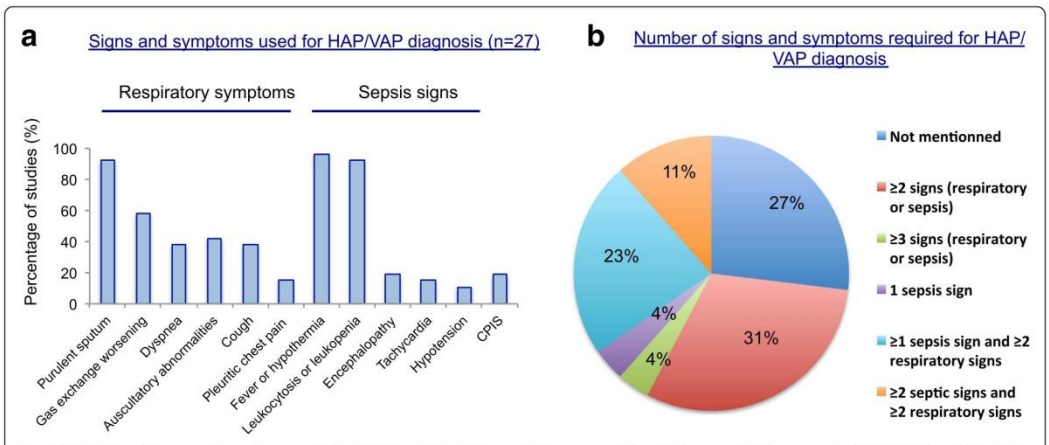


Fig. 2 Variability of signs and symptoms used for definition of hospital-acquired pneumonia/ventilator-associated pneumonia (*HAP/VAP*) (n = 27 studies). **a** Frequency of signs and symptoms used as HAP/VAP diagnostic criteria. **b** Number of signs and symptoms required for HAP/VAP diagnosis. *CPIS* Clinical Pulmonary Infection Score

and superiority trials, respectively. Of note, a pre-specified statistical hypothesis was lacking in nine studies (33%) and sample size calculation was not mentioned in nine studies (33%).

Primary endpoint

Our work revealed marked heterogeneity among the primary endpoints reported in HAP/VAP trials. A single primary endpoint in one population was reported in 13 studies (48%): a clinical cure in 12 trials (44%), CPIS decrease in 1 trial (4%), and 28-day mortality in 1 (4%).

In seven studies, the clinical cure was analyzed in several populations (two populations in six studies, and three populations in one study) without specifying which one was the primary endpoint. In four studies, the clinical cure and microbiological cure were both reported as the primary endpoint and safety was also added in two studies. Altogether, clinical cure was the primary endpoint (or one of the "primary" endpoints) in 24 studies (89%) and mortality in only 2 studies. The various populations used to analyze clinical cure are displayed in Fig. 3a.

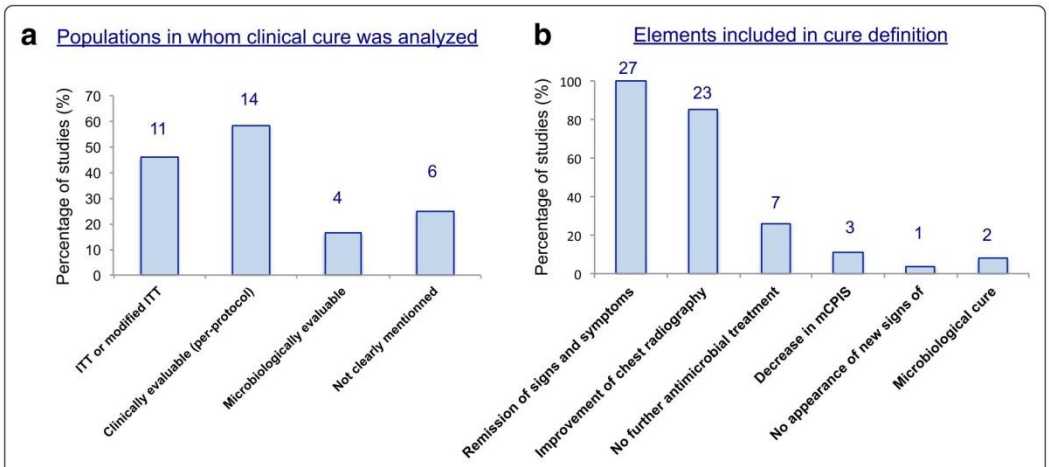


Fig. 3 Clinical cure analysis. **a** Populations in whom clinical cure was analyzed (n = 24 studies. *ITT* intention-to-treat. **b** Items included in the definition of clinical cure. *mCPIS* modified Clinical Pulmonary Infection Score

For a global assessment of study quality, we calculated an 8-point quality score based on 8 systematically evaluated items, reflecting enrollment criteria and methodology (Table 2). Altogether, this score ranged from 2 to 7, thereby confirming the heterogeneity between studies.

Definition of clinical cure and timing of the assessment

Interestingly, elements included in the definition of clinical cure greatly differed among studies (Fig. 3b). Remission of signs and symptoms of pneumonia were included in the definition of clinical cure in all studies, but was only partial in 11 (41%) studies. Chest radiography findings were not systematically taken into account (22 studies, 82%) and they qualified for clinical cure whether the improvement was complete, partial or only a lack of progression in 18 studies (67%). Finally, no need for additional antibiotics during follow up and decrease in the Clinical Pulmonary Infection Score (CPIS) [8] were used in 26% and 11% of studies, respectively. The timing of the TOC visit was different across trials. The time point was between day 7 and day 21 after the end of therapy in 56% percent of the studies; in the remaining trials, it ranged from the end of treatment (4 studies, 15%) till day 30 after treatment (3 studies, 12%). These differences in the definition of clinical cure and in the population and time points used to assess it led to wide variability in reported clinical cure rates that ranged from 23 to 77% (Table 1).

Table 2 Quality assessment of the included randomized controlled trials using eight items and allowing calculation of a quality score

		Enrolment criteria			Methodological quality					
First author	Date	Severity of the population (mean APACHE II >15)	Proportion of patients with VAP mentioned	Microbiological confirmation of HAP/VAP mandatory	Blindness	Clear statistical design	One single endpoint	One single population of interest as primary endpoint	Clear statistical design	**Quality score**
Jaccard	1998	+	-	-	+	-	+	?	-	3
Brun-Buisson	1998	+	+	+	-	+	+	-	+	5
Fagon	2000	-	+	+	-	+	+	+	+	5
Torres	2000	-	-	+	-	-	+	+	-	3
Alvarez-Lerma	2001	+	+	-	-	+	-	-	+	3
Nicolau	2001	-	+	-	-	-	-	+	-	2
Rubinstein	2001	+	+	?	+	+	-	+	+	5
Wunderlink	2003	-	+	+	+	+	-	+	+	5
Zanetti	2003	-	-	-	+	+	-	-	+	2
Shorr	2005	-	+	?	-	-	+	+	-	3
Joshi	2006	-	+	+	+	+	+	+	+	6
Schmidt	2006	-	-	+	+	+	+	+	+	5
Betrosian	2008	-	+	+	-	-	+	+	-	4
Chastre	2008	+	+	-	-	+	+	-	+	4
Giamarallos	2008	+	+	+	+	-	-	-	-	4
Heyland	2008	+	+	-	-	+	+	+	+	5
Freire	2010	-	+	-	+	+	+	-	+	4
Jung	2010	-	+	+	-	+	+	-	+	4
Rattanaumpawan	2010	-	+	+	-	+	-	-	+	3
Lu	2011	+	+	+	-	-	-	-	-	3
Rubinstein	2011	-	+	-	+	+	+	-	+	4
Aydemir	2012	+	+	+	-	-	+	+	-	4
Kollef	2012	-	+	+	+	+	+	+	+	6
Wunderlink	2012	+	+	+	+	+	+	+	+	8
Ramirez	2013	-	+	-	+	+	+	+	+	5
Awad	2014	-	+	?	+	+	+	-	+	4
Kollef	2016	+	+	+	+	-	+	+	-	6

Mortality

All-cause mortality was reported in 22 studies (81%) (primary endpoint in one study) and HAP/VAP-related mortality was reported in 2 studies (Table 1). The time points used to assess mortality were highly variable: day 28 in nine studies, at the end of the study in eight studies, and day 30 and day 60 in four studies and two studies, respectively. At day 28, the mean mortality rate was 23%, with broad variability of the reported all-cause mortality rates from one study to another (range 10–67%; Table 1).

Improvement in methodological quality over time

The methodological quality of studies improved over time. We specifically analyzed the six studies published after the EMA workshop on antimicrobials held in 2011, i.e., between 2012 and 2016. Among the six studies, four had a non-inferiority design (with anticipated statistical approach and non-inferiority margin), were double-blinded, and assessed clinical cure in one population as the single primary endpoint. Clinical criteria for diagnosis of HAP/VAP were more homogenous and at least two clinical signs were consistently required. Furthermore, all cases of pneumonia that were analyzed were microbiologically proven in four of the six trials. Finally, the only items that did not improve were the definition of clinical cure and the time points used to assess it. Calculation of the mean quality score confirmed this global improvement: the mean score of studies published after 2011 was higher than that of older studies (5.3 vs 3.9) (Table 2).

Features of currently unpublished RCTs reported on ClinicalTrials.gov. comparing antimicrobial treatment strategies in HAP/VAP

Thirteen currently unpublished RCTs that tested new antimicrobial treatment strategies in patients with HAP/VAP or with severe infections due to carbapenem-resistant bacteria including HAP/VAP are registered on ClinicalTrials.gov (Table 3). Interestingly, the primary endpoint remained highly variable: 28-day all-cause mortality in four studies (all comparing systemic molecules) and clinical cure (with a variable definition, and using variable timing of assessment) in nine studies (four of them comparing systemic molecules and five testing the efficacy of nebulized antimicrobials) and a favorable clinical response. Only five studies described which population was analyzed.

Discussion

Main findings

In this systematic review comprising 27 published RCTs addressing the efficacy of antimicrobials for treatment of HAP/VAP in critically ill patients, we found that the enrolled populations, clinical trial design, and endpoints assessed vary greatly between studies. This variability is intuitive but its quantification is of importance because, as shown by the variable mortality and clinical cure rates that were reported, it impacted the results of RCTs. This heterogeneity may therefore influence the ability of studies to demonstrate differences between investigational drugs and comparators. These results are not surprising as far as there are even differences in the guidance from regulatory agencies on how to evaluate treatments for HAP/VAP [2, 3], especially with regards to the study design, population and endpoint.

Enrolled populations

In parallel with the inconsistent recommendations of the regulatory agencies on methodology for the diagnosis of HAP/VAP, we found great variability in the clinical criteria used for clinical diagnosis of HAP/VAP. These discrepancies were probably increased by the co-enrollment of patients with HAP and VAP in the majority of studies. Indeed, in agreement with the FDA, but not with the EMA guidelines, no distinction was made between clinical signs and symptoms used for the diagnosis of these different diseases; a minimal duration of mechanical ventilation was required as an inclusion criterion in only 41% of studies. Such a merge of populations with HAP and VAP could mask differences between groups in drug activity, and lead to false conclusions [9]. According to several authors, a combination of clinical and radiological criteria should be used to increase the pretest probability of disease before confirmatory microbiology culture for diagnosis of HAP and VAP [8, 10]. However, in our review, the number of required clinical and biological symptoms greatly varied, and scores combining clinical, biological, and microbiological data such as CPIS [8] were almost never used.

Similarly, in the context of HAP/VAP treatment trials, microbiological confirmation of pneumonia is left optional by the EMA; it was used as inclusion criterion in only 55% of studies included in our review, and among the remaining studies the proportion of microbiologically documented pneumonia varied between 60 and 80%. As a consequence, some patients without pneumonia may have been enrolled in some studies and may have led to false negative results in superiority trials and false conclusions of similarity of drugs in non-inferiority trials. Finally, the severity scores of enrolled patients were very different from one study to another and, in some studies the most severe patients were excluded. The lack of inclusion of some subgroups of patients may be questionable as far as they may specifically receive the maximum benefit of the tested antibiotic [11, 12]. Stratification of randomization of patients based on the severity of illness unfortunately was rarely used.

Table 3 Characteristics of currently unpublished RCTs reported on ClinicalTrials.gov. website, comparing antimicrobials in the management of HAP/VAP

ClinicalTrial.gov identifier	Investigational agent	Comparator	Name of the study	Condition	Primary outcome	Definition of clinical cure	Primary endpoint assessment timing	Analyzed populations	Current status of the study
NCT02714595	S-649266	Best available therapy	CREDIBLE	Severe infections due to carbapenem-resistant GNB including HCAP, HAP and VAP	Clinical cure	1) Resolution or improvement of baseline signs of pneumonia 2) Improvement of chest radiography 3) No additional antibacterial therapy required for current infection treatment	Day 7 after EOT	Not reported	Recruiting
NCT02070757	Ceftolozane/ Tazobactam	Meropenem	ASPECT-NP	VAP or ventilated HAP	All-cause mortality	Not detailed	Day 28	ITT	Recruiting
NCT01808092	Ceftazidime/ Avibactam	Meropenem	REPROVE	HAP/VAP	Clinical cure	1) Patient alive 2) Resolution or improvement of all signs of pneumonia	Day 21 to day 25 after randomization	Co-primary: - clinically ITT - clinically evaluable	Completed-has results
NCT02452047	Imipenem + Cilastatin/ Relebactam	Imipenem + cilastatin +Colistimethate sodium	RESTORE-IMI 1	Severe infections due to Imipenem-resistant bacteria including HAP/VAP	Favorable clinical success	Not specified	Up to day 28	Not reported	Recruiting
NCT02493764	Imipenem +Cilastatin/ Relebactam	Piperacillin/ tazobactam	RESTORE-IMI 2	HAP/VAP	All-cause mortality	Not specified	Day 28	Not reported	Recruiting
NCT01970371	Plazomicin (+meropenem or tigecyclin)	Colistin +Meropenem or Tigecyclin	CARE	Infections due to Carbapenem-resistant *Enterobacteriaceae* including HAP and VAP	All-cause mortality	Not specified	Day 28	Not reported	Completed
NCT02168946	Meropenem Vaborbactam	Best available therapy	Not reported	Infections due to Carbapenem-resistant *Enterobacteriaceae* including HAP and VAP	Clinical cure	Resolution or improvement of the baseline signs and symptoms and no further antimicrobial warranted	Days 12–23	Microbiological ITT	Recruiting
NCT02019420	Tedizolid phosphate	Linezolid	MK-1986-002	Gram-positive HAP/VAP	All-cause mortality	Not specified	Day 28	Microbiological ITT	Recruiting

Table 3 Characteristics of currently unpublished RCTs reported on ClinicalTrials.gov. website, comparing antimicrobials in the management of HAP/VAP *(Continued)*

NCT02440828	Standard treatment + inhaled tobramycin	Standard treatment + Placebo	VAPORISE	VAP	Clinical response	1) Improvement of hypoxemia, 2) Resolution of signs of sepsis 3) No worseming of chest radiography	After 72 hours of treatment	Not reported	Recruiting
NCT02478710	Standard treatment + inhaled tobramycin or inhaled vancomycin	Standard treatment + Placebo	AAINTVAP	VAP	Persistance/recurrence of pneumonia	Not specified	After 8 days of treatment/day 9 to day 21	Not reported	Recruiting
NCT02728518	Standard treatment + nebulized amikacin	Standard treatment + intravenous amikacin	Not reported	GNB-related VAP	Clinical cure	Not specified	Not reported	Not reported	Completed
NCT02574130	Standard treatment + nebulized amikacin	Standard treatment + placebo	Not reported	GNB-related VAP	Clinical cure	No worsening on chest radiography + improvement of leukocytosis and/or fever and/or tracheal secretion	10 days after treatment	Not reported	Recruiting
NCT01799993 and NCT00805168	Standard treatment + amikacin inhalation solution (BAY41-6551)	Standard treatment + placebo	INHALE-1 and 2	GNB-related mechanically ventilated pneumonia	Clinical success	Not specified	28–32 days after treatment initiation	Modified ITT	Recruiting

RCT randomized controlled trial, *HAP* hospital-acquired pneumonia, *VAP* ventilator-associated pneumonia, *ITT* intention-to-treat, *GNB* Gram-negative, *HCAP* Healthcare-associated pneumonia bacilli, *EOT* end of treatment

Design

We identified a large proportion of studies with methodological issues. Although drug dose monitoring or use of multiple antibacterial agents may complicate double-blinding in HAP/VAP studies, it remains crucial to minimize post-randomization bias. In our review, double-blinding was performed in only half of the studies. Furthermore, a pre-specified statistical hypothesis was lacking in more than one study out of four, and the sample size calculation was not mentioned in more than one out of three. Of note, only three studies had superiority design. A statistical hypothesis of non-inferiority was three times more frequent and increased over time (four out of the five most recent studies used it). The use of this design may be the result of FDA and EMA recommendations that describe this design as "acceptable" [2, 3]. Nevertheless, non-inferiority trials are complex to conduct. They require an appropriately selected narrow non-inferiority margin and consequently a large sample size to prevent false conclusions of non-inferiority of the tested drugs. In this context, according to the FDA, mortality non-inferiority margins should be less than 10% [2]. According to the EMA, clinical cure non-inferiority margins should be less than 12.5% [3]. In our study, clinical cure non-inferiority margins were frequently mentioned but they were larger than those recommended in almost all studies, which is clinically unacceptable.

Endpoints

The question of the best primary efficacy endpoint to use in HAP/VAP trials remains highly debatable [13]. Proof of this is provided by the conflicting guidelines provided by the regulatory agencies, with the EMA recommending the clinical outcome at the TOC visit (ranging from 14 to 21 days after the end of therapy) and the FDA recommending all-cause mortality at day 28 [2].

Our results show that the assessment of clinical response (clinical cure) by investigators was used in the vast majority of HAP/VAP RCTs. The main advantage of this criterion is its routine use by clinicians to assess patient response to an antimicrobial treatment. However, as demonstrated by the wide range of clinical cure rates showed in this review, the variable definitions of clinical cure that are used are problematic and may impact the reliability of this endpoint. These results suggest that a consensual definition of clinical cure is urgently needed. Such consensus should also homogenize the timing used to assess the primary endpoint, in order to limit its variability that may also account for variable clinical cure rates. In our review, whatever the endpoint used (i.e., clinical cure or mortality), there was wide variability in the time point used to assess it. Finally, the documentation of the magnitude of treatment effect on clinical cure should also be established. Indeed, a previous demonstration of the superiority of the comparator drug to a placebo or no therapy is necessary before conducting non-inferiority trials [14], and in HAP/VAP such benefit of effective antibacterial therapy has only been established for all-cause mortality [15] and not for clinical cure.

For this reason, mortality is the only endpoint that should be used in non-inferiority trials. However, while mortality is the endpoint that reflects the strongest outcome criteria, its choice may also offer some disadvantages. First, the mortality attributable is difficult to determine; all-cause mortality may be related to underlying comorbidity, affecting the relationship between the efficiency of the antimicrobial treatment and death. Second, low mortality rates reported in HAP/VAP trials (except for those enrolling patients with difficult-to-treat pathogens) and the large non-inferiority margins that are recommended may prevent rejection of the non-inferiority of the tested drug and biased the results.

Nevertheless, the latest FDA recommendations [2] may promote the use of mortality as a primary endpoint. Indeed, among the five currently unpublished RCTs of new systemic molecules that are reported on the ClinicalTrials.gov website, two use 28-day all-cause mortality as the primary endpoint, and one includes death in the definition of clinical cure. Clinical cure was used in seven studies, including one addressing the effect of inhaled antimicrobials as adjunctive therapy. As expected, as a clear consensus is still lacking, the variability in the definition of clinical cure and in the time point used to assess it remain significant.

Conclusion

Altogether, this review provides a description of populations and endpoints of RCTs evaluating antimicrobials for treatment of HAP/VAP in the ICU. Our results show significant heterogeneity in the enrollment criteria, endpoints and statistical design that may influence the ability of studies to demonstrate differences between the drugs studied. Although the methodological quality of studies seems to improve over time, some pitfalls remain. In particular, as demonstrated by the variability observed in currently unpublished RCTs testing new molecules, the regulatory agencies should agree on the best primary endpoint and the timing of its assessment. In this context, composite and/or hierarchical endpoints including both mortality and clinical cure may be of particular interest, and new methodologies helping assess the risks and benefits of new antimicrobial treatment strategies such as desirability of outcome ranking (DOOR) and response adjusted for duration of antibiotic risk (RADAR) may be used [16]. Some other promising new tools such as hierarchical nested design (combining non-inferiority and nested superiority trials) or competing event analyses (considering the influence

of timing of events on effect measures) have also been recently proposed to improve the design and the analysis of future trials [13]. However, some basic concepts such as clinical cure remain to be better defined.

Additional file

Additional file 1: References for studies included in the systematic review. (DOCX 18 kb)

Abbreviations
APACHE: Acute Physiology and Chronic Health Evaluation; CPIS: Clinical Pulmonary Infection Score; DOOR: Desirability of outcome ranking; EMA: European Medicines Agency; FDA: Food and Drug Administration; HAP: Hospital-acquired pneumonia; ICU: Intensive care unit; ITT: Intention to treat; RADAR: Response adjusted for duration of antibiotic risk; RCT: Randomized controlled trial; SAPS: Simplified Acute Physiology Score; TOC: Test of cure; VAP: Ventilator-associated pneumonia

Acknowledgements
The authors thank Celine Feger, MD (EMIBiotech) for her editorial support.

Funding
The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement number 115523 (Combatting Bacterial Resistance in Europe - COMBACTE), resources of which are composed of financial contribution from the European Union's 7th Framework Programme (FP7/2007-2013) and EFPIA companies' kind contribution.

Availability of data and materials
All data generated or analyzed during this study are included in the published articles listed in Additional file 1.

Authors' contributions
EW made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data, and has been involved in drafting the manuscript or revising it critically for important intellectual content. WE made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data. CA made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data. J-RZ made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data, and has been involved in drafting the manuscript or revising it critically for important intellectual content. J-FT made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data, and has been involved in drafting the manuscript or revising it critically for important intellectual content. J-FT also gave final approval of the version to be published. All authors read and approved the final manuscript.

Authors' information
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Consent for publication
Not applicable.

Ethics approval and consent to participate
Not applicable.

Publisher's Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Author details
[1]Department of Anesthesiology and Critical Care, HUPNVS, Hôpital Beaujon, APHP, 92110 Clichy, France. [2]Paris Diderot University, Paris, France. [3]Inserm UMR_S 1149 Center for Research On Inflammation Inserm/University Paris Diderot, Sorbonne Paris Cité, F-75018 Paris, France. [4]UMR 1137 - IAME Team 5 – DeSCID: Decision SCiences in Infectious Diseases, control and care Inserm/University Paris Diderot, Sorbonne Paris Cité, F-75018 Paris, France. [5]Physiology Department, APHP, Hôpital Cochin, Paris, France. [6]Microbiology and infection control unit, APHP, Hôpital Avicenne, Paris, France. [7]Medical and Infectious Intensive Care Unit, AP-HP, Hôpital Bichat Claude Bernard, Paris Diderot University, Paris F-75018, France.

Received: 13 April 2017 Accepted: 6 June 2017
Published online: 27 June 2017

References
1. Nathan C, Cars O. Antibiotic resistance–problems, progress, and prospects. N Engl J Med. 2014;371(19):1761–3.
2. Guidance for Industry Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment. In: U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER); 2014.
3. Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections. In: European Medical Agency; 2013.
4. Richards MJ, Edwards JR, Culver DH, Gaynes RP. Nosocomial infections in medical intensive care units in the United States. National Nosocomial Infections Surveillance System. Crit Care Med. 1999;27(5):887–92.
5. Kalil AC, Metersky ML, Klompas M, Muscedere J, Sweeney DA, Palmer LB, Napolitano LM, O'Grady NP, Bartlett JG, Carratala J, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis. 2016;63(5):e61–e111.
6. Bartlett JG, Barie PS, Niederman MS, Wunderink RG. Workshop on clinical trials of antibacterial agents for hospital-acquired pneumonia and ventilator-associated pneumonia. Clin Infect Dis. 2010;51 Suppl 1:S1–3.
7. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA, Group P-P. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015;349:g7647.
8. Pugin J, Auckenthaler R, Mili N, Janssens JP, Lew PD, Suter PM. Diagnosis of ventilator-associated pneumonia by bacteriologic analysis of bronchoscopic and nonbronchoscopic "blind" bronchoalveolar lavage fluid. Am Rev Respir Dis. 1991;143(5 Pt 1):1121–9.
9. Powers JH. Recommendations for improving the design, conduct, and analysis of clinical trials in hospital-acquired pneumonia and ventilator-associated pneumonia. Clin Infect Dis. 2010;51 Suppl 1:S18–28.
10. Klompas M. Does this patient have ventilator-associated pneumonia? JAMA. 2007;297(14):1583–93.
11. Heyland DK, Dodek P, Muscedere J, Day A, Cook D, Canadian Critical Care Trials G. Randomized trial of combination versus monotherapy for the empiric treatment of suspected ventilator-associated pneumonia. Crit Care Med. 2008;36(3):737–44.
12. Kollef MH. Review of recent clinical trials of hospital-acquired pneumonia and ventilator-associated pneumonia: a perspective from academia. Clin Infect Dis. 2010;51 Suppl 1:S29–35.
13. Timsit JF, de Kraker MEA, Sommer H, Weiss E, Bettiol E, Wolkewitz M, Nikolakopoulos S, Wilson D, Harbarth S, consortium C-N. Appropriate endpoints for evaluation of new antibiotic therapies for severe infections: a perspective from COMBACTE's STAT-Net. Intensive Care Med. 2017. doi:10.1007/s00134-017-4802-4. Epub ahead of print.
14. Infectious Diseases Society of America, American College of Chest Physicians, American Thoracic Society, Society of Critical Care Medicine, Spellberg B, Talbot G. Recommended design features of future clinical trials of antibacterial agents for hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia. Clin Infect Dis. 2010;51 Suppl 1:S150–170.
15. Sorbello AK, Komo S, Valappil T. Noninferiority margin for clinical trials of antibacterial drugs for nosocomial pneumonia. Drug Inf J. 2010;44:165–76.
16. Evans SR, Rubin D, Follmann D, Pennello G, Huskins WC, Powers JH, Schoenfeld D, Chuang-Stein C, Cosgrove SE, Fowler Jr VG, et al. Desirability of outcome ranking (DOOR) and response adjusted for duration of antibiotic risk (RADAR). Clin Infect Dis. 2015;61(5):800–6.

Chapitre 3 : Facteurs de risque de pneumopathies acquises sous ventilation mécanique à germe Gram- négatif résistants, particularités du Stenotrophomonas maltophilia

1) Résumé

Une augmentation de l'incidence des infections nosocomiales dues à des germes résistants, et notamment des BGN, est rapportée dans les dernières recommandations, avec un rôle majeur de l'exposition aux antibiotiques ainsi que la colonisation préalable dans cette augmentation de résistance [4, 5]. Les PAVM causées par des germes multi-résistants sont responsables d'un allongement de la durée de VM et associés à une mortalité plus élevée variant de 23% à 46% selon les études [68, 69]. On note une variabilité du ratio de résistance au niveau des USI de 10% à 25% définissant un haut risque d'acquisition de résistance, conditionnant l'utilisation d'une antibiothérapie plus large ou en association [4, 5, 18]. Cependant, ces chiffres n'ont pas de réel fondement avec un niveau d'épreuve faible, plus basé sur l'observation. Une pression de colonisation à germes résistants de 25% est retenue comme facteur de risque de survenue de résistance dans la seule étude [18]. Partant de cette constatation, nous avons cherché à définir les facteurs de risque de survenue de PAVM à BGN non fermentant et EBLSE ainsi que le ratio de colonisation préalable responsable de l'émergence de résistance en utilisant la base de données OUTCOMEREA.

Sur un total de 1335 épisodes de PAVM enregistrés sur notre période d'étude, 935 épisodes étaient dus à des BGN. Tous les épisodes de PAVM sont confirmés par des prélèvements bactériologiques. On s'est intéressé aussi au recueil de l'exposition préalable aux antibiotiques en calculant le pourcentage de jours d'antibiotiques reçus comme étant le nombre de jours d'antibiotiques reçus avant la survenue de la PAVM sur le nombre de jours d'hospitalisation en réanimation. Le ratio de résistance étant le nombre de patients colonisés par un bacille gram négatif résistant dans un centre donné sur le nombre de patients inclus dans le centre. Un modèle

mixte permettant de tenir compte des événements répétés est utilisé pour nos analyses avec un double effet aléatoire centre et patients. Une infection respiratoire chronique était liée à l'apparition de résistance avec un OR 1.55(1.04-2.32). Les jours d'antibiotiques à large spectre >à 5 jours ou à germe gram négatif >33 jours étaient reliés à une augmentation des résistances de 68% et de 129%. Un ratio de colonisation supérieur à 10 % était corrélé à une augmentation de la résistance dans notre étude. L'adéquation du traitement était de 74.1% pour les PAVM à BGN-S et de 59.6% pour les PAVM à BGN-R (p<0.01).

Nous nous sommes enfin intéressés à un sous-groupe particulier de pathogènes particulièrement résistants aux antibiotiques *S. maltophilia.* Le *stenotrophomonas matophilia* (*SM*) est gram négatif non fermentant, rarement responsable de PAVM, plus présent dans l'arbre bronchique en cas de colonisation. Touchant une population particulière et survenant le plus souvent tardivement. Nous avons dans une analyse cas témoin essayé de différencier les PAVM à SM des autres PAVM sur les facteurs de risques et sur le risque de décès. Deux groupes contrôles ont ainsi été créés. Un groupe de PAVM autre et un groupe de PAVM à *P aeruginosa*. Les cas étaient appariés sur l'hôpital, le SAPSII (± 10%), le délai avant la survenue de la PAVM aux témoins. les groupes ont été comparés avec des tests pour données appariées. Un modèle de Cox marginal tenant compte de l'appariement a été utilisé pour évaluer le risque de décès induit par les PAVM à SM en comparaison des autres PAVM ou des PAVM à *P. aeruginosa*. Nous avons pu montrer que l'exposition préalable à Ureido-carboxypenicillin / Imipenem-Meropenem, ainsi qu'un SOFA score resp/ coag >2 dans les 2 jours avant la survenue de la PAVM, sont des facteurs de risque de survenue de PAVM à *SM*. La mortalité des PAVM à SM est liée à la présence d'une défaillance cardiaque ainsi qu'à l'âge. Nous n'avons pas trouvé d'impact favorable de l'antibiothérapie immédiatement adéquate ou de l'utilisation de combinaisons d'antibiotiques sur le pronostic des PAVM à SM. Enfin, la mortalité des PAVM à SM était supérieure à la mortalité des autres PAVM mais comparable à celle des PAVM à *Pseudomonas aeruginosa*.

2) Article 5 (soumis, Journal of Infection)

Ventilator-associated pneumonia due to *Stenotrophomonas maltophilia*: Risk factors and outcome

Sybille Merceron[1], Wafa ibn saied[2], Carole Schwebel[3], Alban Le Monnier[4], Johana Oziel[5], Maité Garrouste-Orgeas[2,6,8], Guillaume Marcotte[7], Stéphane Ruckly[8], Bertrand Souweine[9], Michael Darmon[10], Lila Bouadma[2,16], Etienne de Montmollin[2,11], Bruno Mourvillier[2,16], Jean Reignier[12], Laurent Papazian[13], Shidasp Siami[14], Elie Azoulay[15], Jean-Pierre Bédos[1], Jean-Francois Timsit [2,8,11]

The manuscript was written on behalf of the OUTCOMEREA study group listed in the appendix.

The 2 first authors SM and WIE contributed equally to the article.

[1] Intensive care Unit Hospital A Mignot, Versailles, France

[2] UMR 1137, IAME, Université Paris Diderot, Paris, France.

[3] Medical Intensive Care Unit, Grenoble University Hospital, Grenoble 1 University, La Tronche, France.

[4] Microbiology Laboratory , Saint Joseph Hospital Network, Paris, France.

[5] Medical surgical ICU, Avicenne hospital, Bobigny, France

[6] Intensive Care Unit, Saint Joseph Hospital Network, Paris, France.

[7] Surgical Intensive Care Unit and Lyon University Hospital, Lyon, France

[8] Outcomerea Research Network, Aulnay sous Bois, France.

[9] Medical Intensive Care Unit, Gabriel Montpied University Hospital, Clermont-Ferrand, France.

[10] Saint Etienne University Hospital, Medical Intensive Care Unit, Saint-Etienne, France

[11] Intensive care medicine, University hospital, Reims, France.

[12] Medical Intensive Care Unit and University Hospital Centre, Nantes,France.

[13] Respiratory and infectious diseases ICU, APHM Hôpital Nord, Aix Marseille University, Marseille, France

[14] Critical Care Medicine Unit CH Etampes-Dourdan, Etampes, France

[15] Intensive Care Unit, Saint Louis Hospital, Paris, France

[16] Medical and Infectious diseases ICU (MI2), APHP, Bichat Hospital, Paris France

Drs. Ibn Saied and Timsit were supported by the Innovative Medicines Initiative Joint Undertaking under grant agreement n [115737-2 – COMBACTE-MAGNET], resources of which are composed of financial contributions from the European Union's Seventh Framework Program (FP7/2007-2013) and EFPIA companies.

The remaining authors have disclosed that they do not have any potential conflicts of interest.

Abstract

Background: *Stenotrophomonas maltophilia* (*SM*) is increasingly identified in intensive care unit (ICU). This study aim to identify risk factors for *SM* ventilator-associated pneumonia (VAP) and whether it affects ICU mortality

Methods: Two nested matched case-control studies were performed based in OUTCOMEREA database. The first episodes of *SM*-VAP patients were matched with two different control groups: VAP due to other micro-organisms (VAP-other) and *Pseudomonas aeruginosa* VAP (Pyo-VAP). Matching criteria were the hospital, the SAPS II, and the previous duration of mechanical ventilation (MV).

Results: Of the 102 *SM*-VAP patients (6.2% of all VAP patients), 92 were matched with 375 controls for the *SM*-VAP/ other-VAP matching and 84 with 237 controls for the *SM*-VAP / *Pyo*-VAP matching. *SM*-VAP risk factors were an exposition to ureido/carboxypenicillin or carbapenem during the week before VAP, and respiratory and coagulation components of SOFA score upper to 2 before VAP. *SM*-VAP received early adequate therapy in 70 cases (68.6%). Risk factors for Day-30 were age (OR=1.03; p <.01) and Chronic heart failure (OR=3.15; p<.01). Adequate treatment, either monotherapy or combination of antimicrobials, did not modify mortality. There was no difference in 30-day mortality, but 60-day mortality was higher in patients with *SM*-VAP compared to Other-VAP (P=0.056).

Conclusions: In a large series, independent risk factors for the *SM*-VAP were ureido/carboxypenicillin or carbapenem exposure the week before VAP, and respiratory and coagulation components of the SOFA score > 2 before VAP. Mortality risk factors of SM-VAP were age and chronic heart failure. Adequate treatment did not improve-*SM*-VAP prognosis.

INTRODUCTION

Stenotrophomonas maltophilia (*SM*) is a non-fermentative gram-negative bacteria involved in Intensive Care Unit (ICU) acquired infections(1, 2), including bloodstream infections, ventilator-associated pneumonia (VAP), skin and soft tissues infections, and rarely urinary tract infections. This ubiquitous bacteria found in water and soil forms biofilms that can enhance its ability to colonize medical devices and lower respiratory tract(2-4). *SM* is naturally highly resistant to most common antibiotics, such as broad-spectrum penicillin including carbapenems, cefepime, or piperacillin-tazobactam, and aminoglycosides. The drug of choice to treat *SM* infections is trimethoprim/sulfamethoxazole (TMX), although strains resistant to TMX are emerging (5, 6). Acquired resistance is also possible through integrons, plasmids, and transposons (3, 4, 7). *SM-VAP* usually occurred after a prolonged duration of mechanical ventilation(3). Although *SM-VAP* represents no more than 6% of all VAP (8, 9), itis associated with high mortality rates, up to 77%(3, 10). A better knowledge of risk factors of *SM*-VAP may allow preventive strategies and adequate early antimicrobial therapy to improve the prognosis.

This study aimed to assess the characteristics of *SM*-VAP in a prospectively collected multicenter medical and surgical ICU setting, to identify risk factors for *SM*-VAP, and to evaluate the outcome of patients.

METHODS AND PATIENTS

We conduct a matched case-control study, based on prospectively collected multicenter French database OUTCOMEREA™ (11). All patients aged over 18 years admitted from 1997 to 2015 presenting at least one episode of VAP were included. Their clinical and biologic data were registered in the database each day of their ICU stay. The French Advisory Committee approved this database collection for Data Processing in Health Research (CCTIRS) and the French Informatics and Liberty Commission (CNIL). The study was approved by the institutional review board of Clermont-Ferrand University, France.

Definition of pneumonia and Antimicrobial Treatment

The diagnosis of VAP was suspected in patients who had received at least 48 hours of mechanical ventilation (MV) and developed a new or persistent infiltrate on chest radiography that was associated with one of the following criteria: (1) purulent tracheal secretions, (2) fever greater than or equal to 38.5°C or hypothermia less than or equal to 36.5°C, and (3) leukocytosis greater than 10^{9}G/L or leukopenia less than 4.10^{8} G/L. The diagnosis of VAP was confirmed by positive quantitative culture of a respiratory sample collected via bronchoalveolar lavage fluid (significant threshold, $\geq 10^{4}$cfu/ml) or plugged telescopic catheter (significant threshold, $\geq 10^{3}$cfu/ml) or protected specimen brush significant threshold, $\geq 10^{3}$cfu/ml) or quantitative endotracheal aspirate (significant threshold, $\geq 10^{5}$ cfu/ml). *SM-VAP* was diagnosed when *SM* was recovered at a significant concentration according to the type of sample.

Treatment was considered adequate when one antimicrobial for which the strain was susceptible *in vitro* was used in the first 24 hours after drawing the bronchial sample. The dose of the antimicrobials was not recorded. Three treatment groups were defined: (1) no adequate treatment within 24 hours defined as untreated *SM*-VAP group; and patients treated adequately within the first 24 hours were split in (2) monotherapy group and (3) combination therapy group.

Data Collection

All relevant data from the medical records including clinical, laboratory, radiology, microbiology information and antibiotic were collected at admission and during the ICU stay (12). Patients were followed until day 60.

Statistical analyses

Characteristics of patients were described as count (percent) or median (interquartile range) for qualitative and quantitative variables, respectively, and were compared between patients' groups using chi-square or Mann-Whitney tests, as appropriate.

We designed two matched cohort analyses: (1) Patients with the first episode of *SM*-VAP were matched (1:n) with patients with VAP due to any other pathogen (other-VAP); (2) Patients with a first episode of *SM*-

VAP were matched (1:n) with patients with *Pseudomonas aeruginosa* VAP (*Pyo*-VAP). The following criteria were used for both matching processes: same ICU, predicted hospital mortality assessed by SAPS II (± 10%), time interval between ICU admission and VAP onset, taking into account the time of VAP occurrence (±1 days if VAP occurs in the 7 first days, ±2 days between the 8th and the 14th days, ±3 days between the 15th and 21st days, ±4 days between the 22nd and the 30th days, ±5 days between the 31st and the 45th days, ±6 days between the 46th and the 60th days, ±7 days between the 61st and the 75th ,±8 days between the 76th and the 90th days). We were able to match 92 cases with 375 controls for the *SM*-VAP/ other-VAP matching and 84 cases with 237 controls for the *SM*-VAP / *Pyo*-VAP matching. We computed the standardized mean differences for each variable to assess the quality of matching.

To identify the risk factors of *SM*-VAP occurrence, matched data were analyzed using conditional logistic regression with stepwise selection. Hematological failure was defined as the hematological component of the SOFA score > 2 on the two days before VAP occurrence.

To identify risk factors of death after *SM*-VAP occurrence, we used survival Cox models. Time zero (T0) was the *SM*-VAP occurrence. Variables identified as significantly associated with mortality by the univariate models were inserted into a multivariate model. A subgroup analysis excluding co-infected *SM*-VAP was also planned. Survival plots were computed. The impact of adequate therapy using monotherapy and combination therapy was tested in the final model values less than 0.05 were considered to be significant. Statistical analyses were performed using SAS 9.4 (Cary, North Carolina, USA).

RESULTS

Epidemiology and clinical features

Among the 1,594 patients with VAP, 102 had at least one episode of *SM*-VAP (***Figure 1).*** *SM*-VAP onset occurred later after ICU admission compared to other-VAP and *Pyo*-VAP (12 [7- 17] days; 10 [6- 15] days and 9 [5- 14] days, respectively). Main characteristics of *SM*-VAP are in **Table 1**. It occurred more frequently in female, with a history of neutropenia, admitted for septic shock and more often associated

with hematological organ failure. Compared to VAP due to other pathogens, *SM*-VAP was associated with significantly higher hospital mortality, and longer ICU stay (32.5 [20- 46] days versus 24 [15- 38] days, respectively (**Table 1**)).

Risk factors of *SM*-VAP

Of the 102 episodes of *SM*-VAP, 92 were successfully matched to 375 patients with VAP due to other pathogens. The quality of the matching procedure was good (***supplemental Figure 1)***. Characteristics of *SM*-VAP and matched controls are on ***Supplemental Table 1***.

The univariate analysis showed that *SM*-VAP remained more frequent in female patients with hematological organ failure and shock. It was associated with an increased previous exposure to antimicrobial therapy and parenteral nutrition. On multivariate analysis, patients with SM-VAP were more frequently female, with a higher SOFA score. Uses of carbapenems and piperacillin-tazobactam within the previous week before VAP were also more frequent (**Table 2)**. Similar results were obtained when SM-VAP were matched to Pyo-VAP (***Supplemental Table 2***).

Adequacy of antimicrobial therapy

SM-VAP was treated adequately in 70 cases (68.6%). The details of the number of patients treated with adequate monotherapy and combination therapy after *SM*-VAP diagnosis is on ***Supplemental Figure* 2 and *Supplemental Table 3*.** Antimicrobial susceptibility testing of *SM* is on ***Supplemental Table 4.***

Mortality of patients with SM-VAP

As compared to the matched other-VAP control group, the mortality rate was higher among patients with *SM*-VAP. But the mortality rate of the *SM*-VAP group was comparable to the mortality of the matched *Pyo*-VAP group (***Figure* 2**). Considering only the *SM*-VAP group, 42 patients (41.2%) died within 30 days after VAP onset. Age and chronic cardiac failures were the only variables associated with *SM*-VAP 30-day mortality (1.02[1.002-1.047] and 2.45[1.12-5.34], respectively **(Table3**)**).** Adequate therapy was not associated with improvement of prognosis regardless of the co-infection (***Supplemental Figure 3***).

DISCUSSION

A total of 102 patients with *SM*-VAP were analysed. To the best of our knowledge, this is the largest cohort of medical and surgical ICU patients with *SM*-VAP ever published.

We found that factors independently associated with *SM*-VAP occurrence were respiratory and coagulation components of the SOFA score > 2 before VAP, and exposure to imipenem and carboxy- or ureido-penicillin within the week before VAP. ICU stay was longer in patients with *SM*-VAP than in patients with VAP due to other pathogens. Risk factors associated with death in *SM*-VAP patients were age and chronic heart failure. Finally, compared to patients with *Pyo*-VAP, patients with *SM*-VAP were more frequently admitted to ICU with neutropenia, had higher median SOFA score at admission, and their first VAP occurred later on. There was no statistical difference in ICU- and hospital length of stay between *Pyo*-VAP and *SM*-VAP and no difference in mortality either.

SM-VAP is a relatively rare occurrence, accounting for 6.4% of all VAP in our study, in line with previous studies (2, 8, 13-17). Patient's characteristics were consistent with other studies of *SM*-VAP (2, 13, 14, 18, 19). The sex-ratio was in favor of male patients in SM-VAP, although the rate of male patients was lower than that in VAP due to other pathogens. Indeed, patients were mainly middle-aged males presenting severe diseases with a median SAPS II of 52. *SM*-VAP occurred in patients with previous long duration of ICU stay and of mechanical ventilation, as compared to other-VAP (2, 14). *SM* is generally considered as an opportunistic pathogen, responsible for late-onset infections in patients with immunosuppression, or undergoing invasive procedures and long-lasting hospitalization(2, 3, 17, 18, 20). Immunosuppression has been described as a significant risk factor for *SM* bacteremia but to our knowledge, not explicitly associated with *SM*-VAP(3, 20).

Importantly, *SM*-VAP is associated with long exposure to broad-spectrum antimicrobials, as reflected in the univariate analysis of our study by the role of the duration of exposure to antibiotics within the week

before the first *SM*-VAP, the median number of antibiotics used at the time of the first *SM*-VAP, and the exposure to broad-spectrum antibiotics such as ciprofloxacin, piperacillin-tazobactam or carbapenems within the week before VAP, in line with previous results (2, 14, 21). Indeed, in a prospective case-control study with 30 *SM* infections including 22 VAP, prior exposure to extended-spectrum cephalosporin was associated with *SM* infection in univariate analysis (2). In another study, only cefepime exposure was significantly associated with *SM*-VAP, but these results could be explained by a large prescription of cefepime in this survey (14). ICU procedures such as catheters, parenteral nutrition, sedation, dialysis, and catecholamine use have also been associated with the risk of *SM*-VAP in the literature (17). Contrarily to previous studies on *SM* bloodstream infections (1, 22), the presence of a central venous catheter and parental nutrition was not associated with *SM*-VAP. It may indeed be explained by differences in pathophysiology of VAP and bloodstream infections, and also because our analysis was matched on patients' severity and ICU length of stay prior to VAP onset. The need for tracheostomy was a significant risk factor for *SM*-VAP in a population of trauma patients, which was not confirmed in our general ICU patient population (14). This may be the result of more severe lung injury in trauma patients with pulmonary contusions which were not observed in our study. Multivariate analysis showed that respiratory failure (PaO2/FiO2 ratio below 300 mmHg) and hematological component of the SOFA score (platelet count below 100G/L) just before VAP onset were strongly associated with the risk of *SM*-VAP.

The crude mortality of *SM*-VAP was higher than the one observed in patients with other VAP, reflecting the fact the disease occurred later in the ICU stay (19, 23). After matching on previous duration of ICU stay, there was no difference in ICU- and day-30 mortality in the two case-control analyses. However, the day-60 mortality was higher in patients with *SM*-VAP compared to other-VAP, but not when compared to Pyo-VAP mortality.

To our knowledge, only one study, on a reduced cohort of six *SM*-VAP patients, assessed day-60 mortality. Mortality rate between *SM*-VAP and other-VAP were not different, which suggests that morbidity and mortality of patients with *SM*-VAP are similar to that of patients with VAP caused by other nosocomial Gram-negative bacilli(13).

Inadequate initial antimicrobial therapy is common for *SM* infections, as this bacteria is naturally resistant to most antibiotics used for the treatment of late-onset nosocomial infections, including carbapenem, piperacillin-tazobactam, and aminoglycosides (18). Moreover, EUCAST (European Committee on Antimicrobial Susceptibility Testing) has provided antimicrobial susceptibility testing breakpoints for only one antibiotic that is trimethoprim-sulfamethoxazole(24). Other antibiotics inconsistently efficient in *SM* infections are ticarcillin-tazobactam, levofloxacin, ciprofloxacin, moxifloxacin, tigecycline, colistin, and ceftazidime (25, 26). Nevertheless, *in vitro* susceptibility rate was high for cotrimoxazole, levofloxacin and colistin with respectively 97%, 94% and 91% of susceptible strains, whereas susceptibility for ticarcillin-clavulanate was only 79%. Overall, 37% patients had an inadequate empirical treatment. While this rate sounds high, it is lower than the one observed in most of the previous studies (1, 2, 14, 18, 27).

We did not find any impact of the adequacy of treatment on *SM*-VAP outcome. Whether the adequacy of the initial therapy has an impact on the outcome in severe late-onset ICU-acquired infections is unclear. In the study of Tseng *et al*., inadequate initial antibiotic therapy was associated with an increased mortality of nosocomial pneumonia due to *SM* (OR=2.17), especially in case of polymicrobial infections(19). On the opposite, recent studies have shown the lack of impact of inadequate initial therapy on patients' outcome in various settings, including bloodstream infections due to *Enterobacteriaceae* and carbapenem-resistant gram-negative bacteria, or *Pseudomonas aeruginosa* VAP (18, 28-30).

Numerous factors could explain this counter-intuitive observation. First, *SM* was not the only recovered pathogen in 31% of the episodes and might be considered as a low pathogen in such VAPs. The coinfection with *P. aeruginosa* and *S. maltophilia* have been reported to impact negatively the prognosis (30). In our study, the treatment of the other pathogens was always adequate and co-infection was not associated with a poorer prognosis. Attributable mortality of *SM*-VAP is still unclear, but the presence of *SM* in the lungs seems to have a deleterious effect on outcome in ICU patients. Second, patients with no clinical signs of severity could have had delayed treatment without any impact on the outcome. Third, treatment regimen, especially doses, could be inadequate in ICU patients with high distribution volumes.

Our study has several strengths. It is the biggest database of medical and surgical patients with *SM*-VAP. We used a high-quality database, with bacteriologically confirmed pneumonia and an audit of all bacteriological results before analyses. We took into account in our matching process the delay before VAP occurrence. For most patients, we recorded long-term follow-up data, making unlikely any bias due to informative censor. We computed the standardized mean differences for each variable to assess the quality of matching. This study has also some limitations. First, the analysis was retrospective, which allows for multiple biases. Second, 31% of *SM*-VAP were polymicrobial; this could have flaw risk factors identification and outcome; however, other studies had a similar approach (14, 31). Third, antibiotic taken before ICU admission were not monitored neither assessed as potential risk factors.

CONCLUSION

In this multicentre retrospective analysis of prospectively collected data from 102 patients with *SM*-VAP, exposure to carbapenem and carboxy- or ureido-penicillin during the week before VAP and the severity of disease with respiratory and hematological failures were independent risk factors for the *SM*-VAP occurrence. Strikingly, the prognosis of patients with *SM*-VAP was not modified by the adequacy of antimicrobial therapy. The prognosis of patients with *SM*-VAP was quite similar to the one of matched other-VAP or *Pyo*-VAP when adjusted on severity at ICU admission and duration of ICU stay before VAP onset.

Acknowledgments: The authors are thankful to Céline Féger, MD (EMIBiotech) for her editorial support.

List of abbreviations:

VAP: Ventilator–acquired pneumonia

ICU: intensive care unit

***SM*-VAP**: *Stenotrophomonas maltophilia* ventilator–acquired pneumonia

Others- VAP: Others microorganisms ventilator–acquired pneumonia

***Pyo*-VAP:** *Pseudomonas aeruginosa* ventilator–acquired pneumonia

Bibliography

1. Fihman V, Le Monnier A, Corvec S, et al. Stenotrophomonas maltophilia--the most worrisome threat among unusual non-fermentative gram-negative bacilli from hospitalized patients: a prospective multicenter study. J Infect 2012;64(4):391-398.

2. Nseir S, Di Pompeo C, Brisson H, et al. Intensive care unit-acquired Stenotrophomonas maltophilia: incidence, risk factors, and outcome. Crit Care 2006;10(5).

3. Looney WJ, Narita M, Muhlemann K. Stenotrophomonas maltophilia: an emerging opportunist human pathogen. Lancet Infect Dis 2009;9(5):312-323.

4. Trifonova A, Strateva T. Stenotrophomonas maltophilia - a low-grade pathogen with numerous virulence factors. Infect Dis 2018;13:1-11.

5. Nicodemo AC, Paez JI. Antimicrobial therapy for Stenotrophomonas maltophilia infections. Eur J Clin Microbiol Infect Dis 2007;26(4):229-237.

6. Wang YL, Scipione MR, Dubrovskaya Y, et al. Monotherapy with fluoroquinolone or trimethoprim-sulfamethoxazole for treatment of Stenotrophomonas maltophilia infections. Antimicrob Agents Chemother 2014;58(1):176-182.

7. Brooke JS. New strategies against Stenotrophomonas maltophilia: a serious worldwide intrinsically drug-resistant opportunistic pathogen: Expert Rev Anti Infect Ther. 2014 Jan;12(1):1-4. doi: 10.1586/14787210.2014.864553. Epub 2013 Dec 4.

8. Chastre J, Fagon JY. Ventilator-associated pneumonia. Am J Respir Crit Care Med 2002;165(7):867-903.

9. Soubirou JF, Gault N, Alfaiate T, et al. Ventilator-associated pneumonia due to carbapenem-resistant Gram-negative bacilli in an intensive care unit without carbapenemase-producing Enterobacteriaceae or epidemic Acinetobacter baumannii. Scand J Infect Dis 2014;46(3):215-220.

10. Paez JI, Tengan FM, Barone AA, et al. Factors associated with mortality in patients with bloodstream infection and pneumonia due to Stenotrophomonas maltophilia. Eur J Clin Microbiol Infect Dis 2008;27(10):901-906.

11. Ibn Saied W, Mourvillier B, Cohen Y, et al. A Comparison of the Mortality Risk Associated With Ventilator-Acquired Bacterial Pneumonia and Nonventilator ICU-Acquired Bacterial Pneumonia. Critical care medicine 2018.

12. Ibn Saied W, Souweine B, Garrouste-Orgeas M, et al. Respective impact of implementation of prevention strategies, colonization with multiresistant bacteria and antimicrobial use on the risk of early- and late-onset VAP: An analysis of the OUTCOMEREA network. PloS one 2017;12(11):e0187791.

13. Scholte JB, Zhou TL, Bergmans DC, et al. Stenotrophomonas maltophilia ventilator-associated pneumonia. A retrospective matched case-control study. Infect Dis 2016;48(10):738-743.

14. Hanes SD, Demirkan K, Tolley E, et al. Risk factors for late-onset nosocomial pneumonia caused by Stenotrophomonas maltophilia in critically ill trauma patients. Clin Infect Dis 2002;35(3):228-235.

15. Guyot A, Turton JF, Garner D. Outbreak of Stenotrophomonas maltophilia on an intensive care unit. J Hosp Infect 2013;85(4):303-307.

16. Sader HS, Farrell DJ, Flamm RK, et al. Antimicrobial susceptibility of Gram-negative organisms isolated from patients hospitalised with pneumonia in US and European hospitals: results from the SENTRY Antimicrobial Surveillance Program, 2009-2012. Int J Antimicrob Agents 2014;43(4):328-334.

17. Chang YT, Lin CY, Chen YH, et al. Update on infections caused by Stenotrophomonas maltophilia with particular attention to resistance mechanisms and therapeutic options. Front Microbiol 2015;6(893).

18. Samonis G, Karageorgopoulos DE, Maraki S, et al. Stenotrophomonas maltophilia infections in a general hospital: patient characteristics, antimicrobial susceptibility, and treatment outcome. PloS one 2012;7(5):18.

19. Tseng CC, Fang WF, Huang KT, et al. Risk factors for mortality in patients with nosocomial Stenotrophomonas maltophilia pneumonia. Infect Control Hosp Epidemiol 2009;30(12):1193-1202.

20. Senol E, DesJardin J, Stark PC, et al. Attributable mortality of Stenotrophomonas maltophilia bacteremia. Clin Infect Dis 2002;34(12):1653-1656.

21. Trouillet JL, Chastre J, Vuagnat A, et al. Ventilator-associated pneumonia caused by potentially drug-resistant bacteria. Am J Respir Crit Care Med 1998;157(2):531-539.

22. Boktour M, Hanna H, Ansari S, et al. Central venous catheter and Stenotrophomonas maltophilia bacteremia in cancer patients. Cancer 2006;106(9):1967-1973.

23. Falagas ME, Kastoris AC, Vouloumanou EK, et al. Attributable mortality of Stenotrophomonas maltophilia infections: a systematic review of the literature. Future Microbiol 2009;4(9):1103-1109.

24. Leclercq R, Canton R, Brown DF, et al. EUCAST expert rules in antimicrobial susceptibility testing. Clin Microbiol Infect 2013;19(2):141-160.

25. Farrell DJ, Sader HS, Jones RN. Antimicrobial susceptibilities of a worldwide collection of Stenotrophomonas maltophilia isolates tested against tigecycline and agents commonly used for S. maltophilia infections. Antimicrob Agents Chemother 2010;54(6):2735-2737.

26. Metan G, Uzun O. Impact of initial antimicrobial therapy in patients with bloodstream infections caused by Stenotrophomonas maltophilia: Antimicrob Agents Chemother. 2005 Sep;49(9):3980-1. doi: 10.1128/AAC.49.9.3980-3981.2005.

27. Czosnowski QA, Wood GC, Magnotti LJ, et al. Clinical and microbiologic outcomes in trauma patients treated for Stenotrophomonas maltophilia ventilator-associated pneumonia. Pharmacotherapy 2011;31(4):338-345.

28. Zak-Doron Y, Dishon Benattar Y, Pfeffer I, et al. The Association between Empirical Antibiotic Treatment and Mortality in Severe Infections Caused by Carbapenem-Resistant Gram-Negative Bacteria: A Prospective Study. Clin Infect Dis 2018;27(4987600).

29. Sommer H, Timsit JF, von Cube M, et al. The Impact of Early Adequate Treatment on Extubation and Discharge Alive of Patients With Pseudomonas aeruginosa-Related Ventilator-Associated Pneumonia. Critical care medicine 2018;46(10):1643-1648.

30. Yin C, Yang W, Meng J, et al. Co-infection of Pseudomonas aeruginosa and Stenotrophomonas maltophilia in hospitalised pneumonia patients has a synergic and significant impact on clinical outcomes. Eur J Clin Microbiol Infect Dis 2017;36(11):2231-2235.

31. Nseir S, Deplanque X, Di Pompeo C, et al. Risk factors for relapse of ventilator-associated pneumonia related to nonfermenting Gram negative bacilli: a case-control study. J Infect 2008;56(5):319-325.

Figure legends

Figure 1: Population Flowchart

Figure 2: Mortality D-60 in the different VAP groups

Table 1: Baseline characteristics of the different VAP categories

Table 2: Risk factors for *Stenotrophomonas maltophilia* VAP

Table 3: Risk factors of 30-day and 60-day mortality in *Stenotrophomonas maltophilia* VAP

Table 1: Baseline characteristics according to the type of VAP

Characteristic's	Other- VAP n=1 492	*SM*-VAP n=102	*Pyo*-VAP n=549	*P**	*P***
Age, median (IQR)	65 [53 - 74]	62 [52 - 75]	66 [53 - 75]	0.52	0.25
Male gender	1051 (70.4)	62 (60.8)	396 (72.1)	0.04	0.02
Diagnosis at the ICU admission (*missing n=12*)					
Organ Failure	64 (4.3)	4 (4)	25 (4.6)	<.01	<.01
Septic shock	179 (12.1)	24 (23.8)	77 (14.1)	.	.
Hemorrhagic shock	49 (3.3)	7 (6.9)	17 (3.1)	.	.
Cardiogenic shock	70 (4.7)	2 (2)	21 (3.8)	.	.
Others shock	33 (2.2)	1 (1)	13 (2.4)	.	.
Respiratory distress	535 (36.1)	37 (36.6)	216 (39.6)	.	.
COPD exacerbation	60 (4.1)	1 (1)	29 (5.3)	.	.
Acute renal failure	37 (2.5)	6 (5.9)	9 (1.6)	.	.
Coma	302 (20.4)	9 (8.9)	87 (15.9)	.	.
Continuous monitoring	89 (6)	8 (7.9)	33 (6)	.	.
Scheduled surgery	44 (3)	2 (2)	13 (2.4)	.	.
Trauma	19 (1.3)	0 (0)	6 (1.1)		
Co-morbidities	733 (49.1)	52 (51)	285 (51.9)	0.72	0.86
Chronic Hepatic failure	101 (6.8)	8 (7.8)	27 (4.9)	0.68	0.23
Chronic Heart failure	234 (15.7)	11 (10.8)	79 (14.4)	0.18	0.33
Chronic Respiratory failure	287 (19.2)	18 (17.6)	125 (22.8)	0.69	0.25
Chronic Renal failure	74 (5)	7 (6.9)	29 (5.3)	0.40	0.52
Chronic Immunodeficiency	247 (16.6)	20 (19.6)	95 (17.3)	0.42	0.58
Aplasia	31 (2.1)	6 (5.9)	10 (1.8)	0.01	0.01
Corticosteroids	95 (6.4)	6 (5.9)	35 (6.4)	0.85	0.85
Chemotherapy	106 (7.1)	9 (8.8)	44 (8)	0.52	0.78
HIV non AIDS	2 (0.1)	0 (0)	2 (0.4)	0.71	0.54
AIDS	38 (2.5)	1 (1)	11 (2)	0.32	0.48
Other	4 (0.3)	1 (1)	0 (0)	0.21	0.02
Transplant	29 (1.9)	3 (2.9)	11 (2)	0.49	0.55
Medical admission category	1119 (75.3)	75 (75.8)	426 (77.6)	0.91	0.69
SAPS II score at the admission , median (IQR)	49 [37 - 62]	52 [40 - 65]	50 [38 - 63]	0.11	0.25
GLASGOW effective (missing n=105)	8 [3 - 14]	7 [3 - 14]	8 [4 - 15]	0.26	0.08
SOFA scoring , median (IQR)	8 [5 - 10]	8.5 [6 - 12]	8 [5 - 10]	<.01	0.01
Respiratory component	2 [2 - 3]	3 [2 - 3]	2 [2 - 3]	0.52	0.78
Cardiovascular component	3 [1 - 4]	3 [1 - 4]	3 [1 - 4]	<.01	0.02
Neurological component	1 [0 - 3]	0 [0 - 3]	1 [0 - 3]	0.93	0.86
Liver component	0 [0 - 1]	0 [0 - 1]	0 [0 - 1]	0.13	0.06
Kidney component	0 [0 - 2]	0 [0 - 2]	1 [0 - 2]	0.74	0.88
Coagulation component	0 [0 - 1]	0 [0 - 2]	0 [0 - 1]	0.05	0.03
ICU admission to first VAP time (days)	9 [5 - 14]	12 [7 - 17]	10 [6 - 15]	<.01	0.03
Duration of ICU stay after the First VAP (days)	13 [7 - 24]	16.5 [8 - 33]	16 [9 - 31]	0.04	0.99
ICU overall length of stay (days)	24 [15 - 38]	32.5 [20 - 46]	29 [19 - 45]	<.01	0.37
Hospital length of stay (days), (missing n=64)	40 [24 - 66.5]	43 [30 - 64]	48 [29 - 76]	0.34	0.25
ICU mortality n (%)	473 (31.7)	40 (39.2)	184 (33.5)	0.12	0.27
Hospital mortality n (%)	636 (42.6)	54 (52.9)	242 (44.1)	0.04	0.10

P**:** Chi2 or Mann Whitney test comparing patient with other-VAP vs. SM-VAP ***P:** Chi2 or Mann Whitney Test comparing patient with *Pyo*-VAP vs *SM*-VAP; VAP: ventilator-associated pneumonia; *SM*-VAP: VAP due to *Stenotrophomonas maltophilia*; Pyo-VAP: VAP due to *Pseudomonasaeruginosa*; COPD: Chronic Obstructive Pulmonary Disease- SAPSII score: Simplified Acute Physiology Score- SOFA score: sequential organ failure assessment score

¤**Matching criteria** : same ICU, predicted hospital mortality assessed by SAPS II and delay before VAP

Table 2: Risk factors for ventilator-associated pneumonia due to Stenotrophomonas maltophilia

Variables[1]	OR IC 95%	*P**
SOFA Score 2 days before VAP		
Respiratory systems Score > 2	1.73 [1.02 -2.92]	0.04
Coagulation system Score > 2	2.93 [1.33 -6.48]	<.01
Antibiotic 1 week before VAP occurrence		
ureido/carboxypenicillin	2.08 [1.22 -3.55]	<.01
Carbapenems (Imipenem/meropenem)	3.20 [1.77- 5.79]	<.001

P *: logistic regression stratified in matched pair and selection stepwise for adjustments variables

SOFA score: sequential organ failure assessment score; VAP: ventilator associated penumonia

[1]Tested variables in the multivariate model: **At the admission**: male gender, chronic heart failure; **In the 2 days before VAP occurrence**: accidental extubation and SOFA scoring (coagulation and cardio-vascular); **In the week before VAP occurrence**: Ureido/carboxypenicillin, Glycopeptides, % Antibiotic received, parenteral nutrition, Dialysis, central venous catheter

Table 3: Risk factors of 30-day and 60-day mortality in ventilator-associated pneumonia due to Stenotrophomonas maltophilia

Characteristics	Alive up at Day-30 n=60)	Death before Day-30 (n=42)	HR IC 95%	*P*	Alive Up to Day-60 (n=52)	Death before Day-60 (n=50)	HR IC 95%	*P*
Age, median (IQR)	57 [50 - 69]	67 [60 - 78]	1.03 [1.01-1.05]	<.01	54.5 [48.5 - 64.5]	67.5 [60 - 78]	1.04 [1.02-1.06]	<.01
Male	39 (65)	23 (54.8)	0.65 [0.36-1.2]	0.17	32 (61.5)	30 (60)	0.77 [0.44-1.36]	0.37
Co-morbidities	26 (43.3)	26 (61.9)	1.77 [0.95-3.31]	0.07	22 (42.3)	30 (60)	1.70 [0.96-2.99]	0.07
Chronic Hepatic failure	3 (5)	5 (11.9)	1.59 [0.62-4.03]	0.33	2 (3.8)	6 (12)	1.68 [0.72-3.95]	0.23
Chronic Heart failure	2 (3.3)	9 (21.4)	3.15 [1.49-6.65]	<.01	2 (3.8)	9 (18)	2.71 [1.3-5.62]	<.01
Chronic Respiratory failure	10 (16.7)	8 (19)	1.32 [0.61-2.86]	0.48	9 (17.3)	9 (18)	1.26 [0.61-2.6]	0.53
Chronic Renal failure	5 (8.3)	2 (4.8)	0.65 [0.16-2.7]	0.56	4 (7.7)	3 (6)	0.91 [0.28-2.93]	0.87
Immunodeficiency	10 (16.7)	10 (23.8)	1.39 [0.68-2.82]	0.37	8 (15.4)	12 (24)	1.45 [0.76-2.78]	0.26
Medical admission category	45 (75)	30 (76.9)	1.14 [0.54-2.41]	0.72	40 (76.9)	35 (74.5)	1.04 [0.54-2.01]	0.90
SAPS II score at the admission, median (IQR)	49 [39.5 - 64.5]	58 [41 - 67]	1.01 [1-1.03]	0.11	48.5 [38.5 - 63]	55.5 [42 - 67]	1.01 [1-1.03]	0.12
Glasgow coma scale (missing n=12)	7 [3 - 15]	7 [3 - 13]	0.97 [0.91-1.03]	0.36	7 [3 - 15]	7 [3 - 13]	0.98 [0.92-1.04]	0.43
SOFA score at VAP onset, median (IQR)	8 [6 - 11]	10 [7 - 13]	1.06 [0.99-1.14]	0.12	8 [5.5 - 11]	10 [7 - 13]	1.05 [0.98-1.12]	0.16
Respiratory component	3 [1.5 - 3]	3 [2 - 3]	1.03 [0.82-1.31]	1.03	2.5 [1.5 - 3]	3 [2 - 3]	1.03 [0.83-1.28]	0.80
Cardiovascular component	3 [1 - 4]	4 [3 - 4]	1.15 [0.91-1.45]	0.24	3 [1 - 4]	3 [2 - 4]	1.06 [0.86-1.3]	0.60
Neurological component	0 [0 - 3]	1.5 [0 - 4]	1.11 [0.93-1.31]	0.25	0 [0 - 3]	0.5 [0 - 4]	1.06 [0.91-1.24]	0.44
Liver component	0 [0 - 1]	0 [0 - 2]	1.17 [0.89-1.54]	0.27	0 [0 - 0.5]	0 [0 - 2]	1.18 [0.91-1.52]	0.22
Kidneys component	0 [0 - 2]	0.5 [0 - 3]	1.03 [0.84-1.27]	0.78	0 [0 - 2]	1 [0 - 3]	1.06 [0.88-1.28]	0.53
Coagulation component	0 [0 - 1.5]	0 [0 - 2]	1.07 [0.85-1.36]	0.56	0 [0 - 1.5]	0 [0 - 2]	1.07 [0.86-1.33]	0.56
Treatment modality				0.43				0.56
Not Treated	45 (75)	25 (59.5)	0.71 [0.29-1.74]		38 (73.1)	32 (64)	0.91 [0.38-2.17]	
Monotherapy	9 (15)	11 (26.2)	1.11 [0.41-2.99]		8 (15.4)	12 (24)	1.31 [0.49-3.5]	
Combination therapy	6 (10)	6 (14.3)	1		6 (11.5)	6 (12)	1	

* Cox model; Time zero (T0): the SM-VAP occurrence

SAPSII score: Simplified Acute Physiology Score- **SOFA score**: sequential organ failure assessment score – **VAP:** ventilator-associated pneumonia:

Appendix

MEMBERS OF THE OUTCOMEREA STUDY GROUP

Scientific Committee: Jean-François Timsit (Medical and Infectious Diseases ICU, Bichat-Claude Bernard Hospital, Paris, France; UMR 1137 Inserm –Paris Diderot university IAME, F75018, Paris); Elie Azoulay (Medical ICU, Saint Louis Hospital, Paris, France); Maïté Garrouste-Orgeas (ICU, Saint-Joseph Hospital, Paris, France); Jean-Ralph Zahar (Infection Control Unit, Angers Hospital, Angers, France); Christophe Adrie (ICU, Delafontaine Hospital, Saint Denis, and Physiology, Cochin Hospital, Paris, France); Michael Darmon (Medical ICU, Saint Etienne University Hospital, St Etienne, France); and Christophe Clec'h (ICU, Avicenne Hospital, Bobigny, and UMR 1137 Inserm –Paris Diderot university IAME, F75018, Paris, France).

Biostatistical and Information System Expertise: Jean-Francois Timsit (Medical and Infectious Diseases ICU, Bichat-Claude Bernard Hospital, Paris, France; UMR 1137 Inserm –Paris Diderot university IAME, F75018, Paris); Corinne Alberti (Medical Computer Sciences and Biostatistics Department, Robert Debré Hospital, Paris, France); Adrien Français (Integrated Research Center U823, Grenoble, France); Aurélien Vesin (OUTCOMEREA organization and Integrated Research Center U823, Grenoble, France); Stephane Ruckly (OUTCOMEREA organization and Inserm UMR 1137 IAME, F75018, Paris); Sébastien Bailly (Grenoble university hospital Inserm UMR 1137 IAME, F75018, Paris) and Christophe Clec'h (ICU, Avicenne Hospital, Bobigny, and Inserm UMR 1137 IAME, F75018, Paris, France); Frederik Lecorre (Supelec, France); Didier Nakache (Conservatoire National des Arts et Métiers, Paris, France); and Aurélien Vannieuwenhuyze (Tourcoing, France).

Investigators of the OUTCOMEREA Database: Christophe Adrie (ICU, Delafontaine Hospital, Saint Denis, and Physiology, Cochin Hospital, Paris, France); Bernard Allaouchiche (ICU, Pierre benite Hospital, Lyon, France); Laurent Argaud (Medical ICU, Hospices Civils de Lyon, Lyon, France); Claire Ara-Somohano (Medical ICU, University Hospital, Grenoble, France); Elie Azoulay (Medical ICU, Saint Louis Hospital, Paris, France); Francois Barbier (medical-surgical ICU, Orleans, France), Jean-Pierre Bedos (ICU, Versailles Hospital, Versailles, France); Julien Bohé (ICU, Hôpital Pierre Benite, Lyon France), Lila Bouadma (ICU, Bichat Hospital, Paris, France); Christine Cheval (ICU, Hyeres Hospital, Hyeres, France); Christophe Clec'h (ICU, Avicenne Hospital, Bobigny, France); Michael Darmon (ICU, Saint Etienne Hospital, Saint Etienne, France); Anne-Sylvie Dumenil (Antoine Béclère Hospital, Clamart, France); Claire Dupuis (Bichat hospital and UMR 1137 Inserm –Paris Diderot university IAME, F75018, Paris, France), Jean-Marc Forel (AP HM, Medical ICU, Hôpital Nord Marseille), Marc Gainier (la Timone hospital, Marseille, France), Akim Haouache (Surgical ICU, H Mondor Hospital, Creteil, France); Samir Jamali (ICU, Dourdan, Dourdan Hospital, Dourdan, France); Hatem Kallel (ICU, Cayenne General Hospital, Cayenne, France); Alexandre Lautrette (ICU, G Montpied Hospital, Clermont-Ferrand, France); Guillaume Marcotte (Surgical ICU, Hospices Civils de Lyon, Lyon, France); Bruno Mourvillier (ICU, Bichat Hospital, Paris, France); Benoît Misset (ICU, Saint-Joseph Hospital, Paris, France); Delphine Moreau (ICU, Saint-Louis Hospital, Paris,

France); Bruno Mourvillier (ICU, Bichat Hospital, Paris, France); Laurent Papazian (Hopital Nord, Marseille, France), Benjamin Planquette (pulmonology ICU, George Pompidou hospital Hospital, Versailles, France); Bertrand Souweine (ICU, G Montpied Hospital, Clermont-Ferrand, France); Carole Schwebel (ICU, A Michallon Hospital, Grenoble, France); Nicolas Terzi (Medical ICU, University Hospital Grenoble, Grenoble, France); Gilles Troché (ICU, Antoine Béclère Hospital, Clamart, France); Dany Toledano (ICU, Gonesse Hospital, Gonesse, France); and Eric Vantalon (SICU, Saint-Joseph Hospital, Paris, France).

Study Monitors: Julien Fournier, Caroline Tournegros, Stéphanie Bagur, Mireille Adda, Vanessa Vindrieux, Loic Ferrand, Nadira Kaddour, Boris Berthe, Samir Bekkhouche, Kaouttar Mellouk, Sylvie Conrozier, Igor Theodose, Veronique Deiler, and Sophie Letrou.

Supplemental material

E1: Univariate analyses for risk factors of *Stenotrophomonas maltophilia* ventilator-associated pneumonia as compared to their matched other-pathogens ventilator-associated pneumonia

E2: Univariate analyses for risk factors of *Stenotrophomonas maltophilia* ventilator-associated pneumonia as compared to their matched *Pseudomonas aeruginosa* ventilator-associated pneumonia

E3: Antibiotic adequacy and different antibiotic day of take in monotherapy or combination therapy

E4: Antimicrobial susceptibility testing for *Stenotrophomonas maltophilia* ventilator-associated pneumonia adequately treated

Supplemental *Figure 1*: Matching assessment for *Stenotrophomonas maltophilia* ventilator-associated pneumonia, other pathogens- ventilator-associated pneumonia and *Pseudomonas aeruginosa* ventilator-associated pneumonia

Supplemental Figure 2: *Antibiotic group and death occurrence in Stenotrophomonas maltophilia* ventilator-associated pneumonia

Supplemental Figure 3: *Comparing Day-30 mortality in Stenotrophomonas maltophilia ventilator-associated pneumonia without co-infection (65 episodes) and all Stenotrophomonas maltophilia ventilator-associated pneumonia (102 episodes) according to the treatment group*

3) Article 6 (en cours de soumission)

Risk factors for third-generation cephalosporins-resistant *Enterobacteriaceae* among patients with ventilator –associated pneumonia: a retrospective cohort study

Wafa ibn saied[1], Bertrand Souweine[2], Claire Dupuis[1, 3], Benoit Misset[4], Shidasp Siami[5], Carole Schwebel, [6] Jean-Marie Forel[7], Stéphane Ruckly[1], Michael Darmon[8], Jean Reignier[9], Virginie Laurent[10], Elie Azoulay[11], Johanna Oziel[12], Lila Bouadma[1, 3], Jean-François Timsit[1, 3]

† The manuscript was written on behalf of the OUTCOMEREA study group listed in the appendix

[1] UMR 1137, IAME, Université de Paris, Paris, France
[2] Medical Intensive Care Unit, Gabriel Montpied University Hospital, Clermont-Ferrand, France
[3] AP-HP, Bichat Hospital, Medical and Infectious Diseases Intensive Care Unit, university of Paris, France
[4] Rouen University Hospital, Medical Intensive Care Unit, Rouen, France
[5] Critical Care Medicine Unit CH Etampes-Dourdan, Etampes, France
[6] Medical Intensive Care Unit, Grenoble University Hospital, Grenoble 1 University, La Tronche, France
[7] Respiratory and infectious diseases ICU, APHM Hôpital Nord, Aix Marseille University, Marseille, France
[8] Saint Etienne University Hospital, Medical Intensive Care Unit, Saint-Etienne, France
[9] Medical Intensive Care Unit and University Hospital Centre, Nantes, France
[10] Medical surgical intensive care unit. Centre hospitalier de Versailles ; Le Chesnay
[11] AP-HP, Saint-Louis hospital; Medical ICU, university of Paris, France
[12] APHP, Avicenne hospital; Medical-surgical ICU, Bobigny, France

Abstract

BACKGROUND: There is an urgent need to understand local prevalence of multidrug-resistant (MDR) pathogens for the management of ventilator-associated pneumonia (VAP).

OBJECTIVES: To investigate risk factors for high risk resistant Gram-negative (HRR-GN) VAP, including that caused by third generation resistant Enterobacteriaceae and non-fermentative Gram-negative bacteria.

METHODS: Prospectively collected, high quality data were used for this study. Clinical and bacteriologic data from 17 French intensive care units (ICUs) who contributed to the OUTCOMEREA® database from 1997 to 2016 were studied. All VAPs were confirmed by positive quantitative culture. A generalized mixed model with binomial distribution was built to assess the risk factors for HRR GN-VAP.

RESULTS: We studied 1,335 VAP episodes. This included 935 GN-VAP episodes of which 634 (67.8%) were HRR GN-VAP. Risk factors for HRR GN-VAP included: septic shock or severe sepsis in the first two days of ICU admission (OR=1.42; p=0.03); chronic respiratory diseases (OR=1.57; p=0.028); known colonization or carriage of HRR-GN in the two days before VAP occurrence (OR=2.39; p=0.0003); and previous antibiotic exposure to board-spectrum antibiotics for more than 33% of the duration of admission to ICU (OR=1.64;P=0.0037) and exposure to antibiotics against gram-negative bacteria for more than 5% of the duration of admission to ICU (OR=2.38; p<0.0001). One center-based variable remained in the final model: An HRR-GN infection rate of 10% or more in the ICU. Treatment within 24 h was more frequently adequate in susceptible GN-VAP (223, 74.1%) than HRR GN-VAP (378, 59.6%; p<0.01).

CONCLUSIONS: We identified patient-related risk factors for HRR-GNB including chronic respiratory diseases, admission with septic shock, known colonization, and previous use of broad-spectrum antibiotics and those against Gram-negative organisms. The knowledge of an HRR-GBN infection rate of more than10% in the unit added significant information to the final model. HRR-GNB however, occurs in 42% of cases with non-identified risk factors emphasizing the need for rapid diagnostic tests to detect antimicrobial resistance.

Introduction

The burden of antimicrobial resistance among Gram-negative pathogens has increased worldwide over the last decade. At present more than 28% of *K. pneumonia* isolates in Europe show resistance to

third generation cephalosporins, compared to 23.6% in 2011. Combined resistance to third generation cephalosporins, fluoroquinolones, and aminoglycosides is currently reported in 10–25% of *E. coli* isolates. Of these, the proportion ascertained as extended-spectrum beta-lactamases (ESBL) positive ranged from 71.1% to 100%, with the majority of countries reporting percentages above 90 %. https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/antimicrobial-resistance-europe-2014.pdf .

Recent data implicate MDR pathogens in up to 35% of ventilator-associated pneumonia (VAP) cases, with a negative impact on clinical outcome [1]. In recent years the spread of resistant pathogens has been increasingly described in other settings besides the ICU, such as oncologic and hematologic wards [2, 3] and long-term care facilities [4]. As a result of their resistance to the most common antimicrobials prescribed empirically, MDR-GN bugs have been associated with delays in an adequate antimicrobial treatment, leading to a significant increase in mortality and a prolonged length of in-hospital stay and excess in health-care costs [5].

The international scientific community published new evidence-based guidelines for the management of hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), and health-care-associated pneumonia [6, 7]. The US guidelines for VAP suggest empirical coverage of *P. aeruginosa* and the use of two antipseudomonal agents when the risk of resistance is high. European guidelines recommended the use of antipseudomonal agents in all cases except patients with suspected low risk of resistance and early onset HAP/VAP and in the absence of septic shock.

Due to the growing prevalence of high risk resistant organisms (i.e. nonfermenting Gram-negative bacteria and third generation cephalosporin–resistant Enterobacteriaceae), it is important for clinicians to understand the epidemiology of and risk factors for the occurrence of this resistance. Successful treatment of infections caused by resistant pathogens is particularly challenging, as resistance patterns change with time and large regional and local variations exist [8]. Identification of patients at risk of high risk resistant

bacteria is essential and could potentially improve the management and survival of these patients. We aim to identify these risk factors with a specific focus on antibiotic exposition and colonization.

Patients and methods

Data source

This observational study was conducted using a multicentre longitudinal database created in 1997 and including data from 23 ICUs contributing to the OUTCOMEREA network. The methodology implemented for data collection and quality control has been extensively described elsewhere [10]. Briefly, patients older than 18 years and with an ICU stay of more than 24 h were randomly selected every year from each participating ICU. Data were collected at admission (demographic characteristics, chronic diseases according to *Knaus* definitions, admission features, baseline severity indexes, admission diagnosis, and admission type) and recorded on a daily basis throughout the ICU stay (daily assessment of organ functions, intensive care procedures, iatrogenic events, colonization with MDR pathogens, ICU-acquired infections, antibiotic exposure, final diagnoses of the ICU stay, and vital status at ICU and hospital discharge). These data were prospectively entered into the database through an anonymized electronic case report from using the Vigirea and Rhea software (OutcomeRea Rosny-sous-Bois, France).

Ethical issues

The French Advisory Committee for Data Processing in Health Research (CCTIRS), the French Informatics and Liberty Commission (CNIL), and the Ethics Committee of Clermont-Ferrand University, France approved this database collection and waived the need for signed informed consent from the participants. The patients and their next of kin were however, informed of their inclusion in the database and could decline participation.

Definitions

Ventilator-associated pneumonia

Pneumonia was defined as new or persistent infiltrate on chest radiography that was associated with one of the following criteria: (1) purulent tracheal secretions, (2) fever greater than or equal to 38.5°C or hypothermia less than or equal to 36.5°C, and (3) leukocytosis greater than 10^{9}G/L or leukopenia less than 4.10^{8} G/L . VAP was defined as pneumonia occurring in a patient within 48 hours or more after invasive mechanical ventilation (IMV). Confirmation was by positive quantitative culture of a respiratory sample collected via bronchoalveolar lavage (significant threshold, $>10^{4}$cfu/ml), protected specimen brush or plugged telescopic catheter (significant threshold, $>10^{3}$cfu/ml) or quantitative endotracheal aspirate (significant threshold, $>10^{5}$ CFU/ml).

Colonization and carriage

A peri-rectal sample was collected at admission and weekly thereafter and screened for ESBLE carriage. Any sample positive for extended-spectrum β-lactamase (ESBL) or AmpC-producing *Enterobacteriaceae*, or *Pseudomonas aeruginosa* (MDRPA) resistant to ticarcillin and/or imipenem and /or ceftazidime were recorded as colonization in the database. We assumed that colonized patients remained colonized for the duration of the study period.

Antibiotic adequacy

Empiric treatment received within the first 24 hours after the occurrence of VAP was considered adequate when at least one antimicrobial agent had an *in vitro* effect on each pathogen recovered within 24 h of taking the respiratory sample. The antibiotic therapy was considered adequate but too broad when a narrower pivotal beta-lactam should have been used (according to the Weiss and coworker classification[9]) or when combination therapy was used when one antimicrobial would have been sufficient.

High risk of resistant Gram-negative organisms

All Gram-negative organisms not susceptible to antimicrobials other than ceftriaxone, cefotaxime, moxifloxacin, or levofloxacin were considered as high risk resistant GN (HRR-GN)

ICU-based variables: the rate of high risk resistant GN in ICU

Data on GN carriage and colonization over time from the different sites (blood culture, urinary tract, airway, catheter, and surgical site) was collected. The ICU rate of HRR-GN was defined as the number of colonized or infected patients with HRR-GN in the center divided by the total number of patients included in the center.

Patient-based variables

Antibiotic class: We defined the following four antibiotic classes: 1) Effective against Gram-positive bacteria including macrolides, glycopeptides, fusidic acid, synergistins, and lincosamides; 2) Effective against Gram-negative bacteria but no or moderate activity against anaerobes including cotrimoxazole, fluoroquinolones, aminoglycosides, ceftazidime, and aztreonam; 3) Effective against anaerobes including metronidazole, synergistin, and lincosamides; and 4) Broad-spectrum antibiotics effective against both Gram-negative bacteria and anaerobes including penems, cephems, aminoglycosides, fosfomycin, glycyclines, uréido-carboxypenicillin with or without beta-lactamase inhibitors, and cephalosporins. For each antibiotic group, we calculated previous antibiotic exposure as the number of days of antibiotic taken before VAP occurrence divided by the number of days in ICU multiplied by 100.

Study population

We included only pneumonia episodes where at least one Gram-negative bacteria was cultured. VAP due to *Haemophilus influenza* was excluded from our analyses.

Outcome measures

The primary outcome was the risk factors for HRR-GN VAP. We also compared the length of ICU stay (LOS), MV duration, and 28-day mortality between GN VAP with or without HRR-GN.

Statistical analysis

Data were expressed as median (IQR) for continuous variables and number (percentage) for categorical variables. Comparisons were performed using the Wilcoxon-Mann-Whitney test for continuous variables and the Fisher exact test or $\chi 2$ test for categorical variables, as appropriate. The missing data were imputed using median or mode as appropriate.

A generalized mixed model with binomial distribution was built to assess the risk factors of HRR-GN-VAP. In this model, patient and center were analyzed as a random effect. Variables yielding p values ≤ 0.10 by univariate analysis were entered into a multivariate model. Previous antibiotic exposure was introduced as a dummy variable according to the median value for each class. For the duration of mechanical ventilation before VAP occurrence, four groups were defined based on quartiles. For center-based HRR-GN ICU rate, the three groups were based on the variable distribution and the cut-off proposed by recent recommendations. Sensitivity analyses including VAP due to *Enterobacteriaceae* only was performed. All statistical analyses were carried out using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). A p-value <0.05 was considered statistically significant.

Results

Epidemiology and clinical features

In the OUTCOMEREA® database between 1997 and February 2016 1,355 episodes of VAP were registered. GN-VAP was noted in 935 episodes, of which 634 (67.80%) were HRR-GN episodes ***(Fig1)***. HRR-GN VAP occurred later than susceptible VAP (HRR-GN 8 [5; 13] days vs. no HRR-GN 6 [4; 11] days). **Table 1** summarizes the baseline characteristic of HRR-GN and other GN-VAP. Other GN-VAP was caused by *Escherichia coli* (31.6%), *Klebsiella* (20.3%), and *Enterobacter sp.* (14.6%). *P. aeruginosa* (72.7%) was the

most common germ in HRR-GN VAP followed by *Stenotrophomonas maltophilia* (10.1%), *Enterobacteriaceae* (9.3%), and *Acinetobacter baumannii* (7.1%; **Table 2**).

Risk factors for HRR-GN VAP

Patients admitted for septic shock/severe sepsis (OR=1.43) and those with chronic respiratory failure (OR=1.55) were more likely to develop antibiotic resistance. Colonization with resistant GNB before VAP occurrence doubled the risk of HRR-GN VAP. The ICU rate of HRR-GN was also a major risk factor with a 2.21 times higher risk of HRR-GN VAP in ICUs with a percentage of HRR- GN upper to 10 %.

Previous antimicrobial exposure has a major impact on HRR-GN VAP risk. Strikingly, patients exposed to 5% or more days of antibiotics effective against Gram-negative organisms and 33% or more days of broad-spectrum antibiotics have a 1.69 and 2.29 increased risk respectively **(Table1)**.

We noted that the occurrence of resistance was associated with the number of risks factors registered, especially if two or more risk factors were registered **(Fig 2)**. On the other hand, resistance also occurred in 12 (41, 37%) out of the 29 episodes without an identified risk factor. The inclusion of HRR-GN colonization in either 6-month or 1-year time windows as a patient-based variable was not associated with the HRR-GN VAP risk (data not shown).

A sensitivity analysis focusing on *Enterobacteriaceae* VAP found admission for coma as a protective factor. Previous colonization with MDR-GNB and previous use of broad spectrum antimicrobials for more than 33% of the duration of ICU stay increased the risk of third generation resistant enterobacteriaceae. Risk factors were grossly similar although we were not able to detect any significant added value of center-based variables (***Supplemental Table 1***).

Treatment and outcome

Treatment within 24 h was more frequently adequate in other GN-VAP (223, 74.1%) compared to HRR-GN VAP (378, 59.6%; p<0.01). Treatment was too broad in 93 (14.7%) cases in the HRR-GN VAP group. Initial antibiotic therapy (IAT) was more frequently inadequate in the HRR-GN VAP group (256, 40.4%) than

in the other VAP group (78, 25.9%). No difference was noted when the length of ICU stay (HRR-GN VAP 28 [14;28] days vs. other VAP 28 [13;28]; p=0.16), and MV duration (HRR-GN VAP 18 [12;29] days vs. other VAP 21 [12;32]; p=0.33) were compared. Similarly, no association between resistance and 28-day ICU mortality was observed (p=0.18): 113 (37.5%) in susceptible versus 209 (33%) in HRR-GN VAP.

Discussion

We found in a large multicenter cohort that HRR-GN VAP occurred in 67.8% of all VAP due to Gram-negative bacteria. IAT was more frequently inadequate in the HRR-GN VAP group. Secondly, we found that admission with chronic respiratory failure, septic shock, previous colonization with MDR-GNB two days before GN-VAP occurrence, and previous antibiotic exposure to broad spectrum antimicrobial agents (for more than 33% of days) and to antibiotics against Gram-negative organisms (for more than 5% of days) were patient-related risk factors for HRR-GN VAP. Importantly, previous duration of MV was not independently associated with HRR-GN VAP risk. Lastly, we found that the ICU rate of HRR-GN was the only center-based variable associated with HRR-GN VAP. A cut point of 10% HRR-GN colonization was the most informative.

The European Centre for Disease Prevention and Control reports a high level and increasing trend of antimicrobial resistance in Gram-negative bacteria in Europe. Being aware of the risk factors is relevant for clinicians to establish early and appropriate antimicrobial treatment. Patient-based variables including the use of intravenous antibiotics in the past 90 days, ≥5 days of hospitalization prior to VAP occurrence, septic shock at the time of VAP, acute respiratory distress syndrome (ARDS) before VAP, and acute renal replacement therapy has been associated with an increased risk of resistance in the available literature and recent guidelines [6, 7, 10, 11].

We report similar risk factors although ARDS was not significant in our final multivariate model.

When the model was adjusted for level of antibiotic therapy and period of MV however, there was no difference in microbial cause for a patient admitted with ARDS[12]. The duration of MV before the

occurrence of pneumonia was quite long in MDR (8 vs. 6 days) and was significant only in the univariate analysis. The early onset of pneumonia is no longer considered protective in terms of the occurrence of resistance, as demonstrated more than 20 years ago by Trouillet et al. [11]. In fact, when the overall incidence of HRR pathogen VAP was higher than 25%, the frequency of HRR pathogens in early-onset pneumonia is similar to the overall frequency of MDR pathogens causing nosocomial pneumonia [7]. Our HRR rate was about 68 %.

The prevalence of colonization with resistant Gram-negative organisms is rising steadily in critically ill patient owing to a continuous influx from both community and healthcare ecosystems, with carriage rates at admission currently above 10% in most ICUs [13-16]. The rise of the risk of HRR GNB carriage early in the ICU stay explains why this parameter can no longer be considered a major determinant of antimicrobial choice. Our result is consistent with results recently reported by other groups [7, 17-19].

Similarly, coma upon ICU admission, which is a risk factor of early onset VAP [20], had a protective effect against the occurrence of resistance [21]. In our analyses, this protective relationship was only found for the *Enterobacteriaceae* subgroup.

Prior carriage and/or colonization with third generation cephalosporin-resistant enterobacteriaceae or multi-resistant *P. aeruginosa* was an important risk factor for HRR-GNB VAP in our analysis and confirmed the findings of previous studies[21].

It has been reported that prior rectal carriage with ESBL enterobacteriaceae increases the risk of ESBL infection (OR=50) [22]. Similarly, Kollef et al. found that *P. aeruginosa* VAP was eight times higher in patients with prior *P. aeruginosa* colonization [23]. Previous colonization enrolment has also been reported by other studies, especially with regard to *P. aeruginosa* [24-26]. Of course, the impact of previous colonization will depend on the site that was colonized and the performance of systematic screening. Our database does not distinguish between sites that were previously colonized. In the participating ICUs, ESBL rectal screening was performed weekly but information on previous MDRGNB carriage or colonization was

obtained using only samples collected as part of the patients' care. The absence of systematic screening may explain why the odds ratio for MDR GNB was only 2.4 in the final model.

Admission to a ward with a higher incidence of patients with HRR pathogens is an important risk factor for the occurrence of HRR infection . However, the cut off for deciding if an ICU is at high risk of infection with resistant bacteria is not known and varies from 10 to 20% or 25% [6, 7, 17, 25, 27]. In our analysis, we used a cut off of 10% for the rate of HRR pathogens within a center to maximize the information. Further studies conducted in other countries with different resistance patterns and antimicrobial usage are needed to confirm this result.

IAT was noted in 71.4 % and 59.6% of susceptible and HRR-VAP, respectively, in our study . IAT failure can occur in 72.5% of patients with resistant pathogens [28]. The association of IAT failure with resistant pathogens highlights the urgent need to understand local prevalence of HRR pathogens when selecting IAT for the management of pneumonia.

Previous antibiotic usage, especially broad-spectrum antibiotics and antimicrobials directed against Gram-negative bacteria with minimal impact on anaerobes, was associated with an increase of HRR-GNB VAP.

The relative impact of each family of antimicrobials on the risk of HRR GNB infection is a matter of debate. This impact may occur in two different, non-exclusive ways. Firstly, the selection of HRR-GNB in the microbiome of the ICU patients may secondarily promote HRR-GNB infection. In experimental models, antimicrobials with high activity against anaerobes have been shown to promote intestinal colonization with multi-resistant Gram-negative organisms. Biliary excretion was the other main factor suggested to contribute to bacterial resistance in the gut .[29, 30]. The second way includes the selection of antibiotic resistant bacteria in a previously colonized respiratory tract. Almost all the antimicrobial families are able to promote superinfection to antimicrobial resistant Gram-negative bacteria. This has been found in previous studies for both enterobacteriaceae and *P. aeruginosa* [11, 31]. Irrespective of the main mechanism of antimicrobial selection, we found that the use of antimicrobials with anti-Gram-negative

activity with minimal effect on anaerobes and also broad spectrum antimicrobials were associated with the most important risk of HRR-GNB VAP. Antimicrobials with predominant or exclusive anti-anaerobic activity were associated with HRR-GNB VAP in univariate analysis but not in the final multivariate model.

Resistance was related to the number of risk factors in our series as shown in **Fig 2.** Despite our efforts, the risk of HRR-GNB was still 41% in patients with no risk factor and 37.6% in patients with zero or one risk factor. Other studies have shown similar results; Loeches et al. reported that 50.7% of patients had potentially resistant microorganisms despite the absence of classic risk factors recognized by current guidelines [17]. Therefore, this study emphasizes the need to develop and validate rapid diagnostic tests for the identification of resistance [32-35]. New techniques which combine metagenomics and traditional bacteriologic methods will be implemented in the near future [36].

Our study has many strengths. Firstly, we included cases with a confirmed microbiologic diagnosis only and had a reasonable sample size. Secondly, we used standardized clinical criteria and definition of VAP. Thirdly, we accounted for repeated episodes of VAP and both patient and unit variables in an appropriate mixed model. Several limitations of the present study should also be addressed. First, data on exposure to an antibiotic before ICU admission was not collected. Second, we focused only on the first mechanical ventilation period. Third, the HRR rate observed in French ICU is different from that observed in other countries and continents. Validation of the model in another setting is therefore needed before our results are generalizable.

Conclusion

Resistance is amplified by antibiotic selective pressure, GNB colonization pressure as well as colonization two days before VAP occurrence. The growing risk of multidrug resistant bacterial colonization at ICU admission probably explains why the previous duration of MV is no longer a predictor of HRR-GNB VAP. Importantly, antimicrobial use, especially the previous use of broad-spectrum antimicrobials and the use of antimicrobials active against Gram-negative organisms without activity on anaerobes, was

associated with HRR GNB. Independent of patient-based variables, the overall rate of HRR GNB in one center was associated with HRR GNB VAP. The cut off that appeared to maximize the effect was 10%. Although the model performed well, about 40% of patients without identified risk factors still have HRR GNB VAP emphasizing the need for an early bacteriologic test to improve detection and thus treatment.

References

1. Martin-Loeches I, Torres A, Rinaudo M, Terraneo S, de Rosa F, Ramirez P, Diaz E, Fernandez-Barat L, Li Bassi GL, Ferrer M. Resistance patterns and outcomes in intensive care unit (ICU)-acquired pneumonia. Validation of European Centre for Disease Prevention and Control (ECDC) and the Centers for Disease Control and Prevention (CDC) classification of multidrug resistant organisms. *J Infect* 2015: 70(3): 213-222.
2. Baker TM, Satlin MJ. The growing threat of multidrug-resistant Gram-negative infections in patients with hematologic malignancies. *Leuk Lymphoma* 2016: 57(10): 2245-2258.
3. Gudiol C, Royo-Cebrecos C, Laporte J, Ardanuy C, Garcia-Vidal C, Antonio M, Arnan M, Carratala J. Clinical features, aetiology and outcome of bacteraemic pneumonia in neutropenic cancer patients. *Respirology* 2016: 21(8): 1411-1418.
4. Venkatachalam I, Yang HL, Fisher D, Lye DC, Moi Lin L, Tambyah P, Perl TM. Multidrug-resistant gram-negative bloodstream infections among residents of long-term care facilities. *Infect Control Hosp Epidemiol* 2014: 35(5): 519-526.
5. Zilberberg MD, Shorr AF, Micek ST, Vazquez-Guillamet C, Kollef MH. Multi-drug resistance, inappropriate initial antibiotic therapy and mortality in Gram-negative severe sepsis and septic shock: a retrospective cohort study. *Crit Care* 2014: 18(6): 014-0596.
6. Kalil AC, Metersky ML, Klompas M, Muscedere J, Sweeney DA, Palmer LB, Napolitano LM, O'Grady NP, Bartlett JG, Carratala J, El Solh AA, Ewig S, Fey PD, File TM, Jr., Restrepo MI, Roberts JA, Waterer GW, Cruse P, Knight SL, Brozek JL. Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infect Dis* 2016: 63(5): e61-e111.
7. Torres A, Niederman MS, Chastre J, Ewig S, Fernandez-Vandellos P, Hanberger H, Kollef M, Li Bassi G, Luna CM, Martin-Loeches I, Paiva JA, Read RC, Rigau D, Timsit JF, Welte T, Wunderink R. International ERS/ESICM/ESCMID/ALAT guidelines for the management of hospital-acquired pneumonia and ventilator-associated pneumonia: Guidelines for the management of hospital-acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP) of the European Respiratory Society (ERS), European Society of Intensive Care Medicine (ESICM), European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and Asociacion Latinoamericana del Torax (ALAT). *Eur Respir J* 2017: 50(3): 00582-02017.
8. Timsit JF, Bassetti M, Cremer O, Daikos G, de Waele J, Kallil A, Kipnis E, Kollef M, Laupland K, Paiva JA, Rodriguez-Bano J, Ruppe E, Salluh J, Taccone FS, Weiss E, Barbier F. Rationalizing antimicrobial therapy in the ICU: a narrative review. *Intensive Care Med* 2019: 45(2): 172-189.
9. Weiss E, Zahar JR, Garrouste-Orgeas M, Ruckly S, Essaied W, Schwebel C, Timsit JF. De-escalation of pivotal beta-lactam in ventilator-associated pneumonia does not impact outcome and marginally affects MDR acquisition. Intensive Care Med. 2016 Dec;42(12):2098-2100. doi: 10.1007/s00134-016-4448-7. Epub 2016 Jul 18.
10. Parker CM, Kutsogiannis J, Muscedere J, Cook D, Dodek P, Day AG, Heyland DK. Ventilator-associated pneumonia caused by multidrug-resistant organisms or Pseudomonas aeruginosa: prevalence, incidence, risk factors, and outcomes. *J Crit Care* 2008: 23(1): 18-26.
11. Trouillet JL, Chastre J, Vuagnat A, Joly-Guillou ML, Combaux D, Dombret MC, Gibert C. Ventilator-associated pneumonia caused by potentially drug-resistant bacteria. *American journal of respiratory and critical care medicine* 1998: 157(2): 531-539.
12. Chastre J, Trouillet JL, Vuagnat A, Joly-Guillou ML, Clavier H, Dombret MC, Gibert C. Nosocomial pneumonia in patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1998: 157(4 Pt 1): 1165-1172.

13. Barbier F, Bailly S, Schwebel C, Papazian L, Azoulay E, Kallel H, Siami S, Argaud L, Marcotte G, Misset B, Reignier J, Darmon M, Zahar JR, Goldgran-Toledano D, de Montmollin E, Souweine B, Mourvillier B, Timsit JF. Infection-related ventilator-associated complications in ICU patients colonised with extended-spectrum beta-lactamase-producing Enterobacteriaceae. *Intensive care medicine* 2018: 44(5): 616-626.
14. Grohs P, Podglajen I, Guerot E, Bellenfant F, Caumont-Prim A, Kac G, Tillecovidin B, Carbonnelle E, Chatellier G, Meyer G, Fagon JY, Gutmann L. Assessment of five screening strategies for optimal detection of carriers of third-generation cephalosporin-resistant Enterobacteriaceae in intensive care units using daily sampling. *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases* 2014: 20(11): O879-886.
15. Razazi K, Mekontso Dessap A, Carteaux G, Jansen C, Decousser JW, de Prost N, Brun-Buisson C. Frequency, associated factors and outcome of multi-drug-resistant intensive care unit-acquired pneumonia among patients colonized with extended-spectrum beta-lactamase-producing Enterobacteriaceae. *Annals of intensive care* 2017: 7(1): 61.
16. Derde LPG, Cooper BS, Goossens H, Malhotra-Kumar S, Willems RJL, Gniadkowski M, Hryniewicz W, Empel J, Dautzenberg MJD, Annane D, Aragao I, Chalfine A, Dumpis U, Esteves F, Giamarellou H, Muzlovic I, Nardi G, Petrikkos GL, Tomic V, Marti AT, Stammet P, Brun-Buisson C, Bonten MJM. Interventions to reduce colonisation and transmission of antimicrobial-resistant bacteria in intensive care units: an interrupted time series study and cluster randomised trial. *The Lancet infectious diseases* 2014: 14(1): 31-39.
17. Martin-Loeches I, Deja M, Koulenti D, Dimopoulos G, Marsh B, Torres A, Niederman MS, Rello J, Investigators E-VS. Potentially resistant microorganisms in intubated patients with hospital-acquired pneumonia: the interaction of ecology, shock and risk factors. *Intensive care medicine* 2013: 39(4): 672-681.
18. Koulenti D, Lisboa T, Brun-Buisson C, Krueger W, Macor A, Sole-Violan J, Diaz E, Topeli A, DeWaele J, Carneiro A, Martin-Loeches I, Armaganidis A, Rello J. Spectrum of practice in the diagnosis of nosocomial pneumonia in patients requiring mechanical ventilation in European intensive care units. *Crit Care Med* 2009: 37(8): 2360-2368.
19. Fagon JY, Chastre J, Wolff M, Gervais C, Parer-Aubas S, Stephan F, Similowski T, Mercat A, Diehl JL, Sollet JP, Tenaillon A. Invasive and noninvasive strategies for management of suspected ventilator-associated pneumonia. A randomized trial. *Annals of internal medicine* 2000: 132(8): 621-630.
20. Bornstain C, Azoulay E, De Lassence A, Cohen Y, Costa MA, Mourvillier B, Descorps-Declere A, Garrouste-Orgeas M, Thuong M, Schlemmer B, Timsit JF. Sedation, sucralfate, and antibiotic use are potential means for protection against early-onset ventilator-associated pneumonia. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2004: 38(10): 1401-1408.
21. Depuydt P, Benoit D, Vogelaers D, Decruyenaere J, Vandijck D, Claeys G, Verschraegen G, Blot S. Systematic surveillance cultures as a tool to predict involvement of multidrug antibiotic resistant bacteria in ventilator-associated pneumonia. *Intensive Care Med* 2008: 34(4): 675-682.
22. Detsis M, Karanika S, Mylonakis E. ICU Acquisition Rate, Risk Factors, and Clinical Significance of Digestive Tract Colonization With Extended-Spectrum Beta-Lactamase-Producing Enterobacteriaceae: A Systematic Review and Meta-Analysis. *Crit Care Med* 2017: 45(4): 705-714.
23. Kollef MH, Chastre J, Fagon JY, Francois B, Niederman MS, Rello J, Torres A, Vincent JL, Wunderink RG, Go KW, Rehm C. Global prospective epidemiologic and surveillance study of ventilator-associated pneumonia due to Pseudomonas aeruginosa. *Crit Care Med* 2014: 42(10): 2178-2187.
24. Rello J, Borgatta B, Lisboa T. Risk factors for Pseudomonas aeruginosa pneumonia in the early twenty-first century. *Intensive Care Med* 2013: 39(12): 2204-2206.
25. Venier AG, Gruson D, Lavigne T, Jarno P, L'Heriteau F, Coignard B, Savey A, Rogues AM. Identifying new risk factors for Pseudomonas aeruginosa pneumonia in intensive care units: experience of the French national surveillance, REA-RAISIN. *J Hosp Infect* 2011: 79(1): 44-48.

26. Garrouste-Orgeas M, Chevret S, Arlet G, Marie O, Rouveau M, Popoff N, Schlemmer B. Oropharyngeal or gastric colonization and nosocomial pneumonia in adult intensive care unit patients. A prospective study based on genomic DNA analysis. *Am J Respir Crit Care Med* 1997: 156(5): 1647-1655.
27. Fernandez-Barat L, Ferrer M, De Rosa F, Gabarrus A, Esperatti M, Terraneo S, Rinaudo M, Li Bassi G, Torres A. Intensive care unit-acquired pneumonia due to Pseudomonas aeruginosa with and without multidrug resistance. *J Infect* 2017: 74(2): 142-152.
28. Ryan K, Karve S, Peeters P, Baelen E, Potter D, Rojas-Farreras S, Pascual E, Rodriguez-Bano J. The impact of initial antibiotic treatment failure: Real-world insights in healthcare-associated or nosocomial pneumonia. *J Infect* 2018: 77(1): 9-17.
29. Sullivan A, Edlund C, Nord CE. Effect of antimicrobial agents on the ecological balance of human microflora. *The Lancet infectious diseases* 2001: 1(2): 101-114.
30. Ruppe E, Andremont A. Causes, consequences, and perspectives in the variations of intestinal density of colonization of multidrug-resistant enterobacteria. *Frontiers in microbiology* 2013: 4: 129.
31. Planquette B, Timsit JF, Misset BY, Schwebel C, Azoulay E, Adrie C, Vesin A, Jamali S, Zahar JR, Allaouchiche B, Souweine B, Darmon M, Dumenil AS, Goldgran-Toledano D, Mourvillier BH, Bedos JP. Pseudomonas aeruginosa ventilator-associated pneumonia. predictive factors of treatment failure. *Am J Respir Crit Care Med* 2013: 188(1): 69-76.
32. Gadsby NJ, McHugh MP, Forbes C, MacKenzie L, Hamilton SKD, Griffith DM, Templeton KE. Comparison of Unyvero P55 Pneumonia Cartridge, in-house PCR and culture for the identification of respiratory pathogens and antibiotic resistance in bronchoalveolar lavage fluids in the critical care setting. *European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology* 2019: 38(6): 1171-1178.
33. Lutgring JD, Bittencourt C, McElvania TeKippe E, Cavuoti D, Hollaway R, Burd EM. Evaluation of the Accelerate Pheno System: Results from Two Academic Medical Centers. *Journal of clinical microbiology* 2018: 56(4).
34. Le Dorze M, Gault N, Foucrier A, Ruppe E, Mourvillier B, Woerther PL, Birgand G, Montravers P, Dilly MP, Tubach F, Andremont A, Timsit JF, Wolff M, Armand-Lefevre L. Performance and impact of a rapid method combining mass spectrometry and direct antimicrobial susceptibility testing on treatment adequacy of patients with ventilator-associated pneumonia. *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases* 2015: 21(5): 468 e461-466.
35. Kollef MH, Burnham CD. Ventilator-Associated Pneumonia: The Role of Emerging Diagnostic Technologies. *Semin Respir Crit Care Med* 2017: 38(3): 253-263.
36. Emonet S, Lazarevic V, Leemann Refondini C, Gaia N, Leo S, Girard M, Nocquet Boyer V, Wozniak H, Despres L, Renzi G, Mostaguir K, Dupuis Lozeron E, Schrenzel J, Pugin J. Identification of respiratory microbiota markers in ventilator-associated pneumonia. *Intensive care medicine* 2019.

MEMBERS OF THE OUTCOMEREA STUDY GROUP

***Scientific Committee*:** Jean-François Timsit (Medical and Infectious Diseases ICU, Bichat-Claude Bernard Hospital, Paris, France; UMR 1137 Inserm –Paris Diderot university IAME, F75018, Paris); Elie Azoulay (Medical ICU, Saint Louis Hospital, Paris, France); Maïté Garrouste-Orgeas (ICU, Saint-Joseph Hospital, Paris, France); Jean-Ralph Zahar (Infection Control Unit, Angers Hospital, Angers, France); Christophe Adrie (Physiology, Cochin Hospital, Paris, France); Michael Darmon (Medical ICU, Saint Etienne University Hospital, St Etienne, France); and Christophe Clec'h (ICU, Avicenne Hospital, Bobigny, and UMR 1137 Inserm –Paris Diderot university IAME, F75018, Paris, France).

***Biostatistical and Information System Expertise*:** Jean-Francois Timsit (Medical and Infectious Diseases ICU, Bichat-Claude Bernard Hospital, Paris, France; UMR 1137 Inserm –Paris Diderot university IAME, F75018, Paris); Corinne Alberti (Medical Computer Sciences and Biostatistics Department, Robert Debré Hospital, Paris, France); Adrien Français (Integrated Research Center U823, Grenoble, France); Aurélien Vesin (OUTCOMEREA organization and Integrated Research Center U823, Grenoble, France); Stephane Ruckly (OUTCOMEREA organization and Inserm UMR 1137 IAME, F75018, Paris); Sébastien Bailly (Grenoble university hospital Inserm UMR 1137 IAME, F75018, Paris) and Christophe Clec'h (ICU, Avicenne Hospital, Bobigny, and Inserm UMR 1137 IAME, F75018, Paris, France); Frederik Lecorre (Supelec, France); Didier Nakache (Conservatoire National des Arts et Métiers, Paris, France); and Aurélien Vannieuwenhuyze (Tourcoing, France).

***Investigators of the OUTCOMEREA Database*:** Dr Romain HERNU

Christophe Adrie (ICU, CH Melun, and Physiology, Cochin Hospital, Paris, France); Carole Agasse (medical ICU, university hospital Nantes, France); Bernard Allaouchiche (ICU, Pierre benite Hospital, Lyon, France); Olivier Andremont (ICU, Bichat Hospital, Paris, France); Pascal Andreu (CHU Dijon, Dijon, France); Laurent Argaud (Medical ICU, Hospices Civils de Lyon, Lyon, France); Claire Ara-Somohano (Medical ICU, University Hospital, Grenoble, France); Elie Azoulay (Medical ICU, Saint Louis Hospital, Paris, France); Francois Barbier (medical-surgical ICU, Orleans, France), Déborah Boyer (ICU, CHU Rouen, France), Jean-Pierre Bedos (ICU, Versailles Hospital, Versailles, France); Thomas Baudry (Medial ICU, Edouard Heriot hospital, Lyon France), Jérome Bedel (ICU, Versailles Hospital, Versailles, France), Julien Bohé (ICU, Hôpital Pierre Benite, Lyon France), Lila Bouadma (ICU, Bichat Hospital, Paris, France); Jeremy Bourenne (Réanimation des urgencies, Timone-2; APHM, Marseille, France); Noel Brule (medical

ICU, university hospital Nantes, France); Cédric Brétonnière (medical ICU, university hospital Nantes, France); Christine Cheval (ICU, Hyeres Hospital, Hyeres, France); Julien Carvelli (Réanimation des urgencies, Timone-2; APHM, Marseille, France);Christophe Clec'h (ICU, Avicenne Hospital, Bobigny, France); Elisabeth Coupez (ICU, G Montpied Hospital, Clermont-Ferrand, France); Martin Cour Medial ICU, Edouard Heriot hospital, Lyon France), Michael Darmon (ICU, Saint Etienne Hospital, Saint Etienne, France); Etienne de Montmollin (ICU, Delafontaine Hospital, Saint Denis), Loa Dopeux (ICU, G Montpied Hospital, Clermont-Ferrand, France); Anne-Sylvie Dumenil (Antoine Béclère Hospital, Clamart, France); Claire Dupuis (Bichat hospital and UMR 1137 Inserm –Paris Diderot university IAME, F75018, Paris, France), Jean-Marc Forel (AP HM, Medical ICU, Hôpital Nord Marseille), Marc Gainnier (Réanimation des urgencies, Timone-2; APHM, Marseille, France), Charlotte Garret (medical ICU, university hospital Nantes, France); Dany Goldgran-Tonedano (CH le Raincy-Montfermeil; France); Steven Grangé (ICU, CHU Rouen, France), Antoine Gros (ICU, Versailles Hospital, Versailles, France), Hédia Hammed (CH le Raincy-Montfermeil) ; Akim Haouache (Surgical ICU, H Mondor Hospital, Creteil, France); Romain Hernu (Medical ICU, Hospices Civils de Lyon, Lyon, France); Tarik Hissem (ICU, Eaubonne, France), Vivien Hong Tuan Ha (ICU, CH Meaux, France); Sébastien Jochmans (ICU, CH Melun); Jean-Baptiste Joffredo (ICU, G Montpied Hospital, Clermont-Ferrand, France); Hatem Kallel (ICU, Cayenne General Hospital, Cayenne, France); Guillaume Lacave (ICU, Versailles Hospital, Versailles, France), Virginie Laurent (ICU, Versailles Hospital, Versailles, France); Alexandre Lautrette (ICU, G Montpied Hospital, Clermont-Ferrand, France); Virgine Lemiale (Medical ICU, Saint Louis Hospital, Paris, France); Mathilde Lermuzeaux (ICU, Bichat Hospital, Paris, France) , Guillaume Marcotte (Surgical ICU, Hospices Civils de Lyon, Lyon, France); Jordane Lebut (ICU, Bichat Hospital, Paris, France); Maxime Lugosi (Medical ICU, University Hospital Grenoble, Grenoble, France); Eric Magalhaes (ICU, Bichat Hospital, Paris, France), Sibylle Merceron (ICU, Versailles Hospital, Versailles, France), Bruno Mourvillier (ICU, Bichat Hospital, Paris, France); Benoît Misset (ICU, Saint-Joseph Hospital, Paris, France and Medical ICU CHU Rouen, France); Bruno Mourvillier (ICU, Bichat Hospital, Paris, France); Mathild Neuville (ICU, Bichat Hospital, Paris, France), Laurent Nicolet (medical ICU, university hospital Nantes, France); Johanna Oziel (Medico-surgical ICU, hôpital Avicenne APHP, Bobigny, France), Laurent Papazian (Hopital Nord, Marseille, France), Benjamin Planquette (pulmonology ICU, George Pompidou hospital Hospital, Paris, France); Jean-Pierre Quenot (CHU Dijon, Dijon, France); Aguila Radjou (ICU, Bichat Hospital, Paris, France), Marie Simon (Medial ICU, Edouard Heriot hospital, Lyon France), Romain Sonneville (ICU, Bichat Hospital, Paris, France), Jean Reignier (medical ICU, university hospital Nantes, France); Bertrand Souweine (ICU, G Montpied Hospital, Clermont-Ferrand,

France); Carole Schwebel (ICU, A Michallon Hospital, Grenoble, France); Shidasp Siami (ICU, Eaubonne, France); Roland Smonig (ICU, Bichat Hospital, Paris, France); Gilles Troché (ICU, Antoine Béclère Hospital, Clamart, France); Marie Thuong (ICU, Delafontaine Hospital, Saint Denis, France); Guillaume Thierry (ICU, Saint-Louis Hospital, Paris, France); Guillaume Van Der Meersch –Medical Surgical ICU, university hospital Avicenne), Marion Venot (Medical ICU, Saint Louis Hospital, Paris, France); Sondes Yaacoubi (CH le Raincy-Montfermeil); Olivier Zambon (medical ICU, university hospital Nantes, France);

Study Monitors*: Julien Fournier, Stéphanie Bagur, Mireille Adda, Vanessa Vindrieux, Sylvie de la Salle, Pauline Enguerrand, Vincent Gobert, Stéphane Guessens, Helene Merle, Nadira Kaddour, Boris Berthe, Samir Bekkhouche, Kaouttar Mellouk, Mélaine Lebrazic, Carole Ouisse, Diane Maugars, Christelle Aparicio, Igor Theodose, Manal Nouacer, Veronique Deiler, Fariza Lamara, Myriam Moussa, Atika Mouaci, Nassima Viguier, Theodora Guerekobaya.*

Figure legends

Figure 1: Population Flowchart

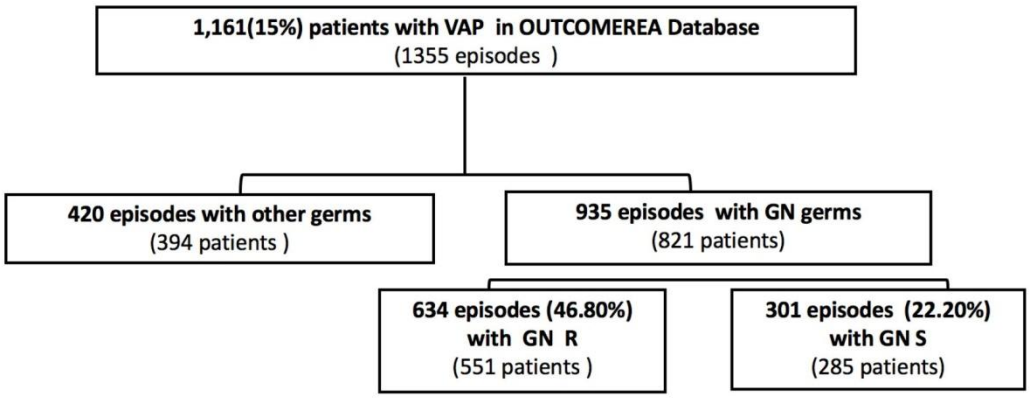
Figure 2: Resistance according to the number of risk factors

Table 1: Baseline characteristic of Gram negative VAP and risk factors for resistance occurrence

Table 2: Microbiological finding in GN-VAP episodes according to the presence or absence of HRR

Supplemental material

Supplemental Table 1: Characteristic and resistant risk factors of *Enterobacteriaceae* VAP



[1] 45 patients had GN (gram negative) and other germs VAP episodes
[2] 15 patients had GN R (resistant gram negative) and GN S (sensitive gram negative) VAP episodes

Figure 1: Flow-chart

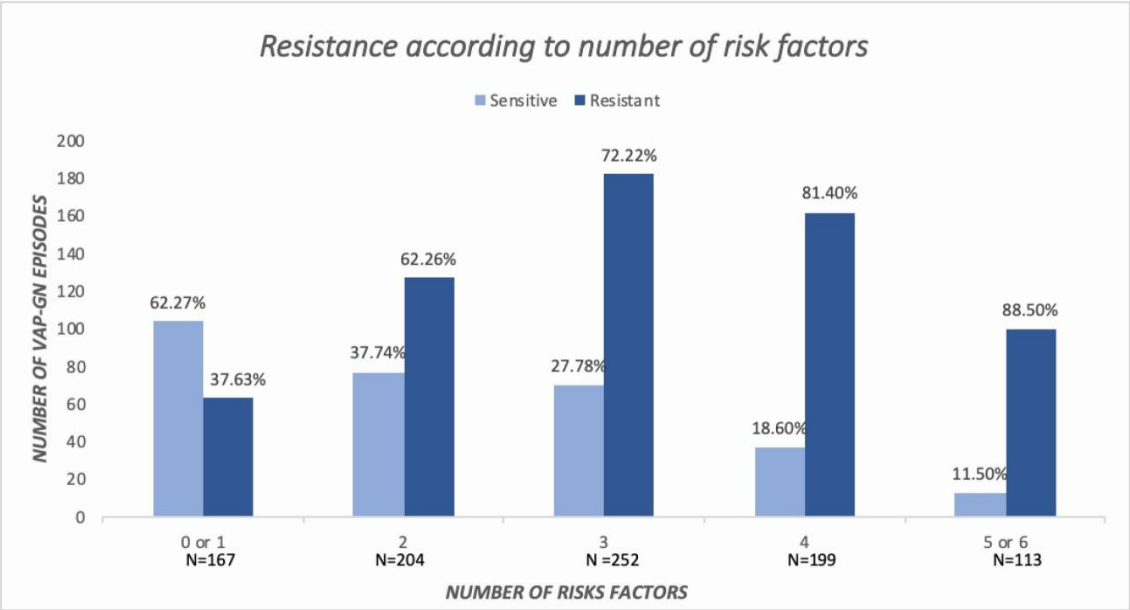


Figure 2: Resistance according to the number of risk factors

Risk factors of HRR-GN VAP (six Risk factors): Chronic Respiratory failure, Septic shock or severe sepsis in the 2 First days of admission in ICU, ICU rate of HRR-GN, BGN colonization 2 days before VAP, Effective against gram-negative bacteria >5 days, Board -spectrum antibiotic >33 days and Rate of HRR-GN≥10 . Resistant GN-VAP rate is related with the number of risks factors noted

Table 1: Baseline characteristic of Gram negative VAP and risk factors of resistance occurrence

Characteristics	Other GN VAP N=301	HRR-GN VAP N=634	Univariate analyses		Multivariate analyses*	
			OR (IC95%)	P value	OR (IC95%)	P value
Patient-based variables						
Male	220 (73.1)	452 (71.3)	0,96[0,69-1,34]	0,8308		
Age (missing n=2)	66 [52.5 ; 75]	66 [54 ; 75]	1,01[1-1,02]	0,2339		
SAPSII	52 [40 ; 63]	49.5 [38 ; 62]	0,99[0,98-1,01]	0.4160		
Comorbidities (Knaus definitions)						
Chronic Hepatic failure	18 (6)	46 (7.3)	1,19[0,65-2,18]	0,5656		
Chronic Heart failure	51 (16.9)	79 (12.5)	0,79[0,51-1,2]	0,2684		
Chronic Respiratory failure	50 (16.6)	144 (22.7)	1,5[1,02-2,2]	0,0395	**1,55[1,04-2,32]**	**0.0314**
Chronic Renal failure	12 (4)	36 (5.7)	1,5[0,74-3,05]	0,2632		
Immunodeficiency	42 (14)	120 (18.9)	1,41[0,92-2,15]	0,1131		
Hospitalization for 24 Hours before transfer in ICU	96 (31.9)	260 (41)	1,57[1,14-2,15]	0,0053		
Admission category						
Medical(*Ref.)*	211 (70.1)	499 (78.7)		0.3056		
Urgent surgery	58 (19.3)	82 (12.9)	1,14[0,67-1,93]			
Scheduled surgery	32 (10.6)	53 (8.4)	0,82[0.45-1.52]			
Coma at the ICU admission	185 (61.5)	358 (56.5)	0,76[0,56-1,03]	0,0816		
Septic shock or severe sepsis in the 2 First days of admission in ICU	147 (48.8)	424 (66.9)	2,02[1,49-2,74]	<,0001		
ARDS in the first days of MV [1]	199 (66.1)	464 (73.2)	1,39[1,01-1,92]	0,0449		
Duration of MV before pneumonia	6 [4 ; 11]	8 [5 ; 13]	1,04[1,02-1,06]	0,0006		
Length of stay before ICU admission	1 [1 ; 3]	2 [1 ; 7]	1,02[1,01-1,04]	0.0080		
Procedures 2 days before VAP						
GNB colonization [2]	28 (9.3)	157 (24.8)	3,16[2,01-4,94]	<,0001	**2,40[1,50-3,82]**	**0.0002**
Chest tube	36 (12)	65 (10.3)	0,9[0,57-1,44]	0,6704		
Extubation	4 (1.3)	6 (0.9)	0,71[0,18-2,75]	0,6157		
Steroids	72 (23.9)	187 (29.5)	1,26[0,9-1,77]	0,1784		
Paralytic agents	29 (9.6)	56 (8.8)	0,91[0,55-1,51]	0,7109		
Dialysis	26 (8.6)	74 (11.7)	1,48[0,89-2,44]	0,127		
Intra hospital transport	26(8 .6)	42(6.6)	0,76[0,44-1,3]	0,3127		

22

Antibiotic class(Number of treatment days per 100 patient days)[3]						
Effective against gram positive bacteria	105 (34.9)	251 (39.6)	1,32[0,97-1,8]	0,0754		
Effective against gram negative bacteria >5 days	113 (37.5)	390 (61.5)	2,61[1,93-3,53]	<,0001	**1,68[1,21-2,35]**	**0.0021**
Effective against anaerobes> 1 day	35 (11.6)	145 (22.9)	2,24[1,47-3,43]	0,0002		
Broad -spectrum antibiotic >33 days	108 (35.9)	408 (64.4)	3,09[2,27-4,22]	<,0001	**2,29[1,64-3,20]**	**<.0001**
ICU-based variables						
ICU rate of High risk resistance GNB [4]				0.0675		**0.0818**
≤10 (*Ref.*)	35 (11.6)	33 (5.2)				
10< Rate of HRR-GN ≤15	46 (15.3)	99 (15.6)	2,09[0,89-4,90]		**1,92[0,89-4,17]**	
Rate of HRR-GN >15	220 (73.1)	502 (79.2)	2,46[1,18-5,14]		**2,20[1,13-4,31]**	

[1] **ARDS**: Acute Respiratory Distress Syndrome;
[2] **GNB colonization**: If extended-spectrum β-lactamase (ESBL) or AmpC-producing -producing Enterobacteriaceae, Pseudomonas aeruginosa (MDRPA) resistant to ticarcillin and/or Imipenem and /or ceftazidime were isolated
[3] **The number of treatment days per 100 patient days**: Total number of antibiotic days before VAP occurrence /total number of days from ICU admission to VAP occurrence ×100;
[4] **ICU rate of High risk resistance GNB:** the percentage of patients with one recovered High risk resistant gram-negative;

Effective against gram-positive bacteria antibiotic: macrolides, glycopeptides, fucidin, synergists, lincosamides
Effective against gram-negative bacteria antibiotic: cotrimoxazole, fluoroquinolone, aminoglycosides, ceftazidime, Aztreonam
Anaerobic antibiotic: Metronidazole, synergistins, lincosamides
Broad-spectrum antibiotic: Penems, Cephems, , Fosfomycin, Glycyclines, Uréido-carboxypenicillin, sulbactam, Tazobactam, cephalosporins

* Multivariate generalized linear mixed model (Variables yielding P values, 0.10 by univariate analysis were entered into a multivariate model: Hospitalization for 24 Hours before transfer in ICU, Coma at the ICU admission, ARDS in the first days of MV, Days of MV before VAP, Effective against gram positive bacteria and Effective against anaerobic antibiotic, Duration of MV before pneumonia, Length of stay before ICU admission). AUC ROC of the final model: 0.815.

23

Table 2: Microbiological finding in GN-VAP episodes according to the presence or absence of MDR

	Other GN N=301	HRR-GN N=634
Enterobacteriaceae		
Escherichia coli	95 (31.6)	38 (6)
Klebsiella	61 (20.3)	31 (4.9)
Proteus, Enterobacter, Serratia, Providencia,and Citrobacter.	145(48.2)	99(15.6)
Nonfermenting gram-negative bacilli		
Acinetobacter baumannii	-	41 (6.5)
Stenotrophomonas maltophilia	-	64 (10.1)
Pseudomonas aeruginosa	-	461 (72.7)
Others Gram-negative microorganisms [1]	22 (7.3)	10 (1.6)
Multigerms [2]	20 (6.6)	100 (15.8)

[1]: *Pseudomonas fluorescens, Pseudomonas putida, Pseudomonas stutzeri, Pseudomonas spp and Other Acinetobacter*
[2]:*VAP GN episodes With more than one micro organisme*
●*P.aeruginosa, A. baumannii, Stenotrophomonas maltophilia* was always defined as resistant gram-negative bacteria.
Enterobacteriaceae not susceptible to third-generation cephalosporins was defined as resistant GN-VAP

Supplemental Table 1: Characteristic and resistant risk factors of *Enterobacteriaceae VAP*

Characteristics	*Enterobacteriaceae* S N=225	*Enterobacteriaceae* R N=134	P*	OR	P**
Patient-based variables					
Male	197 (73.5)	62 (68.1)	0.69		
Age (missing n=2)	66 [51 ; 75]	66 [54 ; 78]	0.55		
Comorbidities (Knaus definitions)					
Chronic Hepatic failure	18 (6.7)	8 (8.8)	0.89		
Chronic Heart failure	45 (16.8)	10 (11)	0.61		
Chronic Respiratory failure	51 (19)	20 (22)	0.66		
Chronic Renal failure	13 (4.9)	4 (4.4)	0.86		
Immunodeficiency	43 (16)	19 (20.9)	0.30		
Admission category					
Medical(*Ref.*)	189 (70.5)	77 (84.6)	0.69		
Urgent surgery	51 (19)	10 (11)			
Scheduled surgery	28 (10.4)	4 (4.4)			
Septic shock or severe sepsis in the 2 First days of admission in ICU	134 (50)	61 (67)	0.082		
Coma at the ICU admission	59 (22)	8 (8.8)	0.001	**0.37 (0.15-0.94)**	**0,04**
ARDS in the first days of MV [1]	176 (65.7)	71 (78)	0.145		
Time before VAP occurrence	7 [4 ; 11]	8 [4 ; 12]	0.223		
Days of MV before VAP					
<5 days	86 (32.1)	23 (25.3)			
5 ≤days of VM≤8	79 (29.5)	28 (30.8)			
9 ≤days of VM≤13	60 (22.4)	20 (22)			
≥14 days (*Ref.*)	43 (16)	20 (22)	0.007		
Procedures 2 days before VAP					
GNB colonization	26 (9.7)	31 (34.1)	<.0001	**4.67 (2.24-9.73)**	**<.0001**
Chest tube	33 (12.3)	4 (4.4)	0.128		
Extubation	4 (1.5)	2 (2.2)	0.615		
Steroids	63 (23.5)	28 (30.8)	0.166		
Paralytic agents	23 (8.6)	12 (13.2)	0.208		
Intra hospital transport	30 (11.2)	9 (9.9)	0.596		
Dialysis	23 (8.6)	8 (8.8)	0.930		
Antibiotic class(Number of treatment days per 100 patient days)[3]					
Effective against gram positive bacteria	93 (34.7)	34 (37.4)	0.321		
Effective against gram negative bacteria >5 days	102 (38.1)	53 (58.2)	.002		
Effective against anaerobie	29 (10.8)	24 (26.4)	0.010		
Broad -spectrum antibiotic >33 percent	105 (39.2)	61 (67)	.0002	**2.42 (1.23-4.64)**	**0.0103**
ICU based variables					
ICU rate of High risk resistance GNB [4]			0.14		
≤17 (*Ref.*)	138(51.5)	44 (48.4)			
>=17 percent	130 (48.5)	47 (51.6)			

[1] **ARDS**: Acute Respiratory Distress Syndrome;
[2] **GNB colonization**: If extended-spectrum β-lactamase (ESBL) or AmpC-producing -producing Enterobacteriaceae, Pseudomonas aeruginosa (MDRPA) resistant to ticarcillin and/or Imipenem and /or ceftazidime were isolated
[3] **The number of treatment days per 100 patient days**: Total number of antibiotic days before VAP occurrence /total number of days from ICU admission to VAP occurrence ×100;
[4] **ICU rate of High risk resistance GNB:** the percentage of patients with one recovered High risk resistant gram-negative;

* Univariate generalized linear mixed model;** multivariate generalized linear mixed model
Effective against gram-positive bacteria antibiotic: macrolides, glycopeptides, Fucidin, synergists, lincosamides
Effective against gram-negative bacteria antibiotic: Bactrim, fluoroquinolone, aminoglycosides, ceftazidime, Aztreonam
Anaerobic antibiotic: Metronidazole, synergists, lincosamides
Broad-spectrum antibiotic: 3rd and 4th cephalosporin,Penems, Cephems, Fosfomycin, Glycyclines, Uréido-carboxypenicillin, sulbactam, Tazobactam

26

Dans cette partie, nous avons synthétisé l'apport des différentes études réalisées dans le cadre de cette thèse en termes de prise en charge de pneumopathie en réanimation. Nous discuterons ensuite des limites que nous avons rencontrées et les manières à développer pour les aborder.

I) PAVM précoces et tardives : est-il utile de continuer à faire cette distinction ?

Il était courant de faire la distinction entre les PAVM d'apparition précoce (dans les quatre premiers jours de VM) et d'apparition tardive (au-delà des quatre jours de VM). En effet, il était commun de penser que les PAVM précoces sont principalement causées par des bactéries gram-négatives sensibles telles que : *Haemophilus influenzae, Staphylococcus aureus sensibles à la méthicilline (SASM) et Streptococcus pneumoniae* alors que les PAVM tardives étaient l'apanage des bactéries gram-négatives résistantes aux antibiotiques de niveau plus élevé, comme *Pseudomonas aeruginosa et Acinetobacter spp.* , ou *S. aureus* résistant à la méthicilline (SARM) [1, 2]. Cette classification ayant mené à des stratégies de traitement empiriques différentes: monothérapie avec antibiotiques à spectre étroit pour le traitement de la pneumonie précoce, et un traitement à large spectre pour les infections tardives visant potentiellement le *Pseudomonas spp*. ou *SARM*. Cependant cette distinction est de plus en plus discutée actuellement.

Plusieurs études confirment l'absence de différence entre les pathogènes responsables de PAVM précoce et tardive. Pour Gastmeier et al dans une étude multicentrique de plus de 300 services de réanimation avec plus 16 000 cas de pneumopathie nosocomiale dont 87,4% étaient des PAVM, pas de différences dans les pathogènes retrouvés dans les PAVM précoces et tardives [20]. Ce résultat se maintenait avec la variation du `cut-off` utilisé pour la définition de EOP (4ème jour, 5ème jour et 7ème jour de VM) ainsi qu'on faisait des analyses en sous-groupe selon le moyen diagnostic (aspiration trachéale ou lavage broncho alvéolaire) et par période en tenant compte du

changement de la définition des pneumopathies nosocomiales par le CDC en 2005. Ce résultat est confirmé par d'autres études [70-72]. Dans une étude comparant les patients ayant une PAVM précoce et PAVM tardive, Mosconi et al ne trouvent pas de différence dans la proportion de germes résistants et le risque de décès entre PAVM précoce et tardive [73].

L'apparition de résistance semble plutôt liée à l'exposition préalable aux antibiotiques, la durée d'hospitalisation préalable, la colonisation préalable et des facteurs environnementaux spécifiques au service de réanimation [1, 74]. La prévalence de germe résistant varie à travers les pays, les hôpitaux et les services de soins [75]. Les dernières recommandations mettent plus l'accent sur l'importance de l'environnement et de la colonisation préalable dans l'apparition d'infection à germe résistant. En effet, une bi thérapie visant *Peudomonas aeruginosa* est recommandée dans le traitement des PAVM en première intention si l'unité de soin a un taux de résistance élevé. La définition d'un taux élevé de résistance dans les unités varie d'un consensus à l'autre et reflète l'absence de données précises dans la littérature. Un taux de BGN résistant supérieur à 10% est utilisé par le consensus Américain [4]. Selon le consensus Européen, une prévalence de germe résistant (BGN et le SARM) dans une unité de soin >25 % représente une situation à risque élevé de survenue d'une infection à germes résistants et nécessitant une bithérapie adaptée. Dans ces 2 consensus le niveau d'épreuve étant faible avec une seule étude ayant montré le lien entre la prévalence des bactéries multi résistantes et la survenue d'infection à germe résistant [18]. Les recommandations Françaises de SFAR-SRLF, quant à elle, préconisent plutôt un seuil de 20% [30].

Notre étude plaide plus pour l'utilisation d'un seuil de 10% dans les réanimations françaises. La disparité de l'épidémiologie de la résistance d'un pays à l'autre est telle que ce résultat ne doit pas être extrapolé directement à d'autres systèmes de soins. Les autres critères justifiant l'utilisation d'un traitement anti gram négatif à large spectre reste la colonisation préalable, l'exposition aux antibiotiques à large spectre. La présence d'un choc septique et d'un

SDRA en particulier chez des patients avec des maladies chroniques respiratoires ou les immunodéprimés encourage aussi à une combinaison antibiotique large active sur *P aeruginosa*. La place de *S.maltophilia* dans le choix antibiotique initial est limitée. Elle doit être réservée aux patients présentant une PAVM très tardive déjà exposés aux carbapénèmes ou à un traitement anti-gram négatif à large spectre prolongé.

II) Pneumopathies liées aux soins: nouveau défi diagnostique et thérapeutique

Les taux d'incidence des PAVM diminuent, tandis que les diagnostics cliniques et la prescription d'antibiotiques demeurent élevés. Cette disparité reflète l'absence de critères objectifs et de définition uniformisée pour diagnostiquer les PAVM [76]. Riaz et al, dans une étude sur 319 patients avec suspicion clinique de PAVM, comparaient le diagnostic clinique à celui retenu après les résultats de la culture semi-quantitative ou quantitative du LBA. Selon les critères diagnostics retenus, ce nombre diminue progressivement, passant de 319 cas (suspicion clinique seulement) à 235 cas (culture positive semi quantitative ou quantitative) à 84 cas (culture quantitative $>10^5$ UC/ml sur LBA)[77]. Nous avons confirmé l'extrême hétérogénéité des critères diagnostiques de PAVM et de ICU-HAP dans les essais randomisés de réanimation. Sur les 27 essais cliniques randomisés sélectionnés, seulement 55% exigeaient une confirmation microbiologique. La définition de la guérison clinique reposait aussi sur des critères divers en fonction des études.

L'imprécision des définitions d'infection pulmonaire entraine une incertitude sur l'efficacité des thérapeutiques et peut en partie expliquer l'absence de bénéfice franc de l'adéquation de l'antibiothérapie dans les pneumonies acquises en réanimation en particulier chez le patient non ventilé [78].

Il est aussi possible que le délai diagnostique des techniques microbiologiques traditionnelles soit déjà trop long. Le traitement immédiatement adéquat est donc déjà trop tardif. Les outils de diagnostic de biologie moléculaire en cours de développement pourraient permettre une amélioration considérable dans un avenir proche [79, 80]. Ces nouveaux tests

réduisent considérablement le temps d'identification (entre 1,5 h à 6 h) comparativement aux méthodes de culture classiques. Cependant les techniques moléculaires fournissent une information partielle sur la susceptibilité aux antibiotiques. En effet, un nombre limité de gènes de résistance acquis sont testés (CTX-M ou Carbapenemase pour les BGN). Leur impact clinique sur le délai de prise en charge et le pronostic des pneumonies nosocomiales n'a pas encore été évalué [81].

L'absence d'impact de l'adéquation du traitement antibiotique peut aussi être le fait de l'absence d'optimisation de la pharmacodynamie des antibiotiques utilisés. En effet, on confond souvent un traitement antibiotique efficace in vitro avec un traitement antibiotique efficace pour traiter la pneumonie nosocomiale. Le sous dosage en antibiotique est fréquent chez les patients septiques. En effet, un patient sur six recevant les bêta-lactamines n'atteint pas la CMI [82]. Ceci est particulièrement inquiétant dans les premières heures de thérapie lorsqu'un effet maximal est hautement souhaitable. Ce sous-dosage peut être expliqué par plusieurs facteurs, tout d'abord la difficulté de déterminer le volume de distribution chez un patient en sepsis ou sous épuration extra-rénale. De plus, de nombreux antibiotiques utilisés ont une élimination rénale, et entrainent l'utilisation de posologies initiales insuffisantes en cas d'insuffisance rénale [83]. Troisièmement, il a été montré qu'il existait une variabilité interindividuelle en termes de PK.

Pour obtenir des taux d'antibiotiques efficaces, il faut probablement utiliser des posologies élevées même en cas d'insuffisance rénale. En effet, le volume de distribution ne dépend pas de la clairance. Il faut de plus exploiter les propriétés pharmacocinétiques et pharmacodynamiques des familles d'antibiotiques disponibles. Une dose élevée initiale quelle que soit la clairance est probablement à privilégier [84]. L'impact de la délivrance des antibiotiques en perfusion prolongée ou continue pour les beta-lactamines est suggéré par certaines études mais reste à démontrer. Le dosage des concentrations sériques d'antibiotiques en réanimation a une importance capitale, permettant d'éviter le sous-dosage ou les surdosages dangereux.

La place des modèles PK/PD ou des logiciels de prédiction pour utiliser la dose appropriée est délicate du fait de la très grande variabilité intra et inter-individuelle en réanimation.

III) Optimisation du traitement des PAVM à germes gram négatif : comment prédire le risque d'infection à germes potentiellement résistants

En plus de la lutte contre la diffusion des bactéries multi-résistantes en réanimation, il convient de choisir un traitement antibiotique immédiatement efficace tout en évitant l'utilisation d'antibiothérapie à large spectre quand une antibiothérapie plus étroite serait efficace.

Il est donc fondamental d'identifier précocement les patients à hauts risques de résistance antibiotique. Divers scores ont été explorés dans le but de développer des méthodes efficaces pour diagnostiquer la résistance. Malheureusement, l'intérêt de ces scores reste limité [85]. La plupart des cliniciens se basent lors de la prescription d'antibiotiques à large spectre sur des faisceaux d'arguments tels que: l'hospitalisation préalable en réanimation, ou en soins de suite et réhabilitation, l'exposition récente aux antibiotiques, ce qui mène à une prescription peu spécifique et vaste [18, 86-90].

Les éléments les plus fréquemment rapportés sont :

Le terrain : La présence de plusieurs co-morbidités à tendance à allonger la durée de séjour. L'utilisation de procédure invasive ainsi que l'augmentation préalable de l'exposition aux antibiotiques augmentant ainsi le risque d'infection à germes résistants [91, 92]. L'âge des patients lors de la survenue d'infection est associé à une mortalité plus importante ainsi qu'à la survenue de complications. Ceci est probablement dû à la présence de pathologies chroniques récurrentes, au retard diagnostic et thérapeutique et à une incidence plus élevée d'infection nosocomiale chez cette population.

La colonisation préalable à germes résistants : La colonisation amplifie considérablement le risque d'infection subséquente à un germe multi-résistant. Toutefois, la valeur prédictive positive

de ce facteur de risque ne dépasse jamais 50 % quel que soit le germe colonisateur [93-96]. En effet, les infections à EBLSE surviennent pendant le séjour aux soins intensifs chez seulement 10 à 25 % des porteurs de EBLSE [97]. Cependant, une autre étude a montré que l'incidence d'infection à *Pseudomonas aeruginosa* était de 26% chez les colonisés préalablement, versus 5% chez les non porteurs (P<0.001)[65]. La question étant de savoir si les facteurs liés à l'infection et à la colonisation sont les mêmes ou différents [93-95]. La présence ou l'absence de portage documenté ne devrait pas être considéré comme la condition unique pour le choix de l'antibiothérapie.

Les caractéristiques de l'unité de soins: Le service d'hospitalisation du patient est un autre déterminant du risque. En effet, il y a de grandes différences dans l'épidémiologie des germes résistants à l'échelle mondiale, régionale et même au sein des hôpitaux d'une même ville [95, 98]. Ces écarts peuvent être imputables aux facteurs socioéconomiques, la pression de sélection des antibiotiques ainsi que l'implantation des règles d'hygiène limitant la transmission croisée.

L'utilisation préalable des antibiotiques : reste la cause favorisante la plus fréquente de la résistance bactérienne. L'ensemble des catégories d'antibiotiques favorisent l'émergence de la résistance bactérienne par la pression de sélection. Le mécanisme est le plus souvent la sélection de bactéries non sensibles aux antibiotiques dans les microbiotes et une infection secondaire. La sélection de mutants résistants dans le site infecté est un phénomène plus rare.

IV) Pronostic des pneumopathies liées aux soins

La survenue de pneumonie nosocomiale en réanimation est associée à un risque de décès. La mortalité attribuable est difficile à déterminer mais semble plus importante en cas de pneumonies à bactéries résistantes, si les patients ont une gravité intermédiaire et si le traitement est inadéquat. Cependant, le lien entre la résistance et le pronostic reste débattu. En effet dans une étude incluant 510 patients avec une septicémie à *Entérobactérie* résistantes, Burnham et al ont montré que la résistance n'était pas corrélée à la gravité du sepsis si le traitement initial est

adapté [99]. Ce résultat est confirmé par une autre étude, mettant l'accent sur l'importance de l'adéquation de l'antibiothérapie initiale [100].

Peu d'études se sont intéressées à la mortalité liée à l'ICU-HAP. Cependant, celle-ci entraine une ventilation mécanique dans un tiers des cas et sont associées à un choc septique dans 20% des cas. Le risque de décès des ICU-HAP nécessitant la ventilation mécanique est même plus élevé que celui des PAVM [7]. Le sur-risque de décès induit par les ICU-HAP dans notre étude confirme l'importance pronostique majeure des ICU-HAP.

Conclusions et Perspectives

Les analyses réalisées pendant cette thèse ont permis de raffiner les connaissances sur les facteurs de risque de PAVM en identifiant des facteurs de risque différents pour les PAVM précoces et tardives. Les PAVM précoces semblent plus accessibles à la prévention.

Notre travail montre l'impact majeur des ICU-HAP survenant en réanimation chez le patient non ventilé qui justifie des travaux complémentaires afin de permettre une identification et un diagnostic étiologique précoce et une prévention satisfaisante. La tendance à l'utilisation préférentielle de stratégies non invasives de ventilation pourrait d'ailleurs amplifier le phénomène dans les années prochaines.

Notre travail met aussi en évidence l'extrême difficulté du pari antibiotique dans la pneumopathie acquise en réanimation. Un traitement antibiotique large couvrant *P aeruginosa* et les autres BGN potentiellement résistants aux antibiotiques est recommandé dans la plupart des cas et expose à la sur-utilisation des antibiotiques de réserve. En conséquence, un effort de diagnostic étiologique et d'identification de résistance précoce est nécessaire pour traiter de manière adéquate en utilisant des molécules à trop large spectre.

Références

1. Chastre, J. and J.Y. Fagon, *Ventilator-associated pneumonia.* Am J Respir Crit Care Med, 2002. **165**(7): p. 867-903.
2. *Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia.* Am J Respir Crit Care Med, 2005. **171**(4): p. 388-416.
3. Rello, J., J. Riera, and R. Serrano, *What's new in ventilator-associated pneumonia?* Intensive Care Med, 2015. **41**(11): p. 1954-6.
4. Kalil, A.C., et al., *Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society.* Clin Infect Dis, 2016. **63**(5): p. e61-e111.
5. Torres, A., et al., *International ERS/ESICM/ESCMID/ALAT guidelines for the management of hospital-acquired pneumonia and ventilator-associated pneumonia: Guidelines for the management of hospital-acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP) of the European Respiratory Society (ERS), European Society of Intensive Care Medicine (ESICM), European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and Asociacion Latinoamericana del Torax (ALAT).* Eur Respir J, 2017. **50**(3): p. 00582-2017.
6. Villar, J., et al., *The ALIEN study: incidence and outcome of acute respiratory distress syndrome in the era of lung protective ventilation.* Intensive Care Med, 2011. **37**(12): p. 1932-41.
7. Talbot, G.H., *Evolution and current status of United States Food and Drug Administration and European Medicines Agency regulatory guidance for studies of nosocomial pneumonia.* Curr Opin Crit Care, 2018. **24**(5): p. 379-384.
8. Magill, S.S., et al., *Multistate point-prevalence survey of health care-associated infections.* N Engl J Med, 2014. **370**(13): p. 1198-208.
9. Reignier, J., et al., *Impact of early nutrition and feeding route on outcomes of mechanically ventilated patients with shock: a post hoc marginal structural model study.* Intensive Care Med, 2015. **41**(5): p. 875-86.
10. Vincent, J.L., et al., *International study of the prevalence and outcomes of infection in intensive care units.* JAMA, 2009. **302**(21): p. 2323-9.
11. Wang, Y., et al., *National trends in patient safety for four common conditions, 2005-2011.* N Engl J Med, 2014. **370**(4): p. 341-51.
12. Blot, S., et al., *Prevalence, risk factors, and mortality for ventilator-associated pneumonia in middle-aged, old, and very old critically ill patients*.* Crit Care Med, 2014. **42**(3): p. 601-9.
13. Koulenti, D., et al., *Spectrum of practice in the diagnosis of nosocomial pneumonia in patients requiring mechanical ventilation in European intensive care units.* Crit Care Med, 2009. **37**(8): p. 2360-8.
14. Metersky, M.L., et al., *Trend in Ventilator-Associated Pneumonia Rates Between 2005 and 2013.* Jama, 2016. **316**(22): p. 2427-2429.
15. Park, D.R., *The microbiology of ventilator-associated pneumonia.* Respir Care, 2005. **50**(6): p. 742-63.
16. Trouillet, J.L., et al., *Ventilator-associated pneumonia caused by potentially drug-resistant bacteria.* Am J Respir Crit Care Med, 1998. **157**(2): p. 531-9.
17. Ferrer, M., et al., *Validation of the American Thoracic Society-Infectious Diseases Society of America guidelines for hospital-acquired pneumonia in the intensive care unit.* Clin Infect Dis, 2010. **50**(7): p. 945-52.

18. Martin-Loeches, I., et al., *Potentially resistant microorganisms in intubated patients with hospital-acquired pneumonia: the interaction of ecology, shock and risk factors.* Intensive Care Med, 2013. **39**(4): p. 672-81.
19. Martin-Loeches, I., et al., *Resistance patterns and outcomes in intensive care unit (ICU)-acquired pneumonia. Validation of European Centre for Disease Prevention and Control (ECDC) and the Centers for Disease Control and Prevention (CDC) classification of multidrug resistant organisms.* J Infect, 2015. **70**(3): p. 213-22.
20. Gastmeier, P., et al., *Early- and late-onset pneumonia: is this still a useful classification?* Antimicrob Agents Chemother, 2009. **53**(7): p. 2714-8.
21. Restrepo, M.I., et al., *Comparison of the bacterial etiology of early-onset and late-onset ventilator-associated pneumonia in subjects enrolled in 2 large clinical studies.* Respir Care, 2013. **58**(7): p. 1220-5.
22. Melsen, W.G., et al., *Attributable mortality of ventilator-associated pneumonia: a meta-analysis of individual patient data from randomised prevention studies.* Lancet Infect Dis, 2013. **13**(8): p. 665-71.
23. Valles, J., et al., *Efficacy of single-dose antibiotic against early-onset pneumonia in comatose patients who are ventilated.* Chest, 2013. **143**(5): p. 1219-25.
24. Bornstain, C., et al., *Sedation, sucralfate, and antibiotic use are potential means for protection against early-onset ventilator-associated pneumonia.* Clin Infect Dis, 2004. **38**(10): p. 1401-8.
25. Visscher, S., et al., *Effects of systemic antibiotic therapy on bacterial persistence in the respiratory tract of mechanically ventilated patients.* Intensive Care Med, 2008. **34**(4): p. 692-9.
26. de Jonge, E., et al., *Effects of selective decontamination of digestive tract on mortality and acquisition of resistant bacteria in intensive care: a randomised controlled trial.* Lancet, 2003. **362**(9389): p. 1011-6.
27. Kollef, M.H., *Broad-spectrum antimicrobials and the treatment of serious bacterial infections: getting it right up front.* Clin Infect Dis, 2008. **15**(47): p. 590061.
28. Tumbarello, M., et al., *Clinical outcomes of Pseudomonas aeruginosa pneumonia in intensive care unit patients.* Intensive Care Med, 2013. **39**(4): p. 682-92.
29. Iregui, M., et al., *Clinical importance of delays in the initiation of appropriate antibiotic treatment for ventilator-associated pneumonia.* Chest, 2002. **122**(1): p. 262-8.
30. Leone, M., et al., *Hospital-acquired pneumonia in ICU.* Anaesth Crit Care Pain Med, 2018. **37**(1): p. 83-98.
31. Pugin, J., et al., *Diagnosis of ventilator-associated pneumonia by bacteriologic analysis of bronchoscopic and nonbronchoscopic "blind" bronchoalveolar lavage fluid.* Am Rev Respir Dis, 1991. **143**(5 Pt 1): p. 1121-9.
32. Torres, A., et al., *Sampling methods for ventilator-associated pneumonia: validation using different histologic and microbiological references.* Crit Care Med, 2000. **28**(8): p. 2799-804.
33. Torres, A. and M. El-Ebiary, *Bronchoscopic BAL in the diagnosis of ventilator-associated pneumonia.* Chest, 2000. **117**(4 Suppl 2): p. 198S-202S.
34. *A randomized trial of diagnostic techniques for ventilator-associated pneumonia.* N Engl J Med, 2006. **355**(25): p. 2619-30.
35. Fagon, J.Y., et al., *Invasive and noninvasive strategies for management of suspected ventilator-associated pneumonia. A randomized trial.* Ann Intern Med, 2000. **132**(8): p. 621-30.
36. Sole Violan, J., et al., *Impact of quantitative invasive diagnostic techniques in the management and outcome of mechanically ventilated patients with suspected pneumonia.* Crit Care Med, 2000. **28**(8): p. 2737-41.

37. Bonten, M.J., et al., *Implementation of bronchoscopic techniques in the diagnosis of ventilator-associated pneumonia to reduce antibiotic use.* Am J Respir Crit Care Med, 1997. **156**(6): p. 1820-4.
38. Timsit, J.F., et al., *Usefulness of a strategy based on bronchoscopy with direct examination of bronchoalveolar lavage fluid in the initial antibiotic therapy of suspected ventilator-associated pneumonia.* Intensive Care Med, 2001. **27**(4): p. 640-7.
39. Leone, M., et al., *Empirical antimicrobial therapy of septic shock patients: adequacy and impact on the outcome.* Crit Care Med, 2003. **31**(2): p. 462-7.
40. Pileggi, C., et al., *Prevention of ventilator-associated pneumonia, mortality and all intensive care unit acquired infections by topically applied antimicrobial or antiseptic agents: a meta-analysis of randomized controlled trials in intensive care units.* Crit Care, 2011. **15**(3).
41. Nseir, S., et al., *Continuous control of tracheal cuff pressure and microaspiration of gastric contents in critically ill patients.* Am J Respir Crit Care Med, 2011. **184**(9): p. 1041-7.
42. Muscedere, J., et al., *Subglottic secretion drainage for the prevention of ventilator-associated pneumonia: a systematic review and meta-analysis.* Crit Care Med, 2011. **39**(8): p. 1985-91.
43. Bouadma, L., et al., *Long-term impact of a multifaceted prevention program on ventilator-associated pneumonia in a medical intensive care unit.* Clin Infect Dis, 2010. **51**(10): p. 1115-22.
44. Goossens, H., et al., *Outpatient antibiotic use in Europe and association with resistance: a cross-national database study.* Lancet, 2005. **365**(9459): p. 579-87.
45. Esperatti, M., et al., *Nosocomial pneumonia in the intensive care unit acquired by mechanically ventilated versus nonventilated patients.* Am J Respir Crit Care Med, 2010. **182**(12): p. 1533-9.
46. Herer, B., et al., *Management of nosocomial pneumonia on a medical ward: a comparative study of outcomes and costs of invasive procedures.* Clin Microbiol Infect, 2009. **15**(2): p. 165-72.
47. Azoulay, E., et al., *Diagnostic strategy for hematology and oncology patients with acute respiratory failure: randomized controlled trial.* Am J Respir Crit Care Med, 2010. **182**(8): p. 1038-46.
48. Salahuddin, N., et al., *Determinants of Deescalation Failure in Critically Ill Patients with Sepsis: A Prospective Cohort Study.* Crit Care Res Pract, 2016. **6794861**(10): p. 14.
49. Kollef, M.H., et al., *Epidemiology and outcomes of health-care-associated pneumonia: results from a large US database of culture-positive pneumonia.* Chest, 2005. **128**(6): p. 3854-62.
50. Russell, C.D., et al., *Diagnosis and features of hospital-acquired pneumonia: a retrospective cohort study.* J Hosp Infect, 2016. **92**(3): p. 273-9.
51. Weber, D.J., et al., *Microbiology of ventilator-associated pneumonia compared with that of hospital-acquired pneumonia.* Infect Control Hosp Epidemiol, 2007. **28**(7): p. 825-31.
52. Brito, V. and M.S. Niederman, *Healthcare-associated pneumonia is a heterogeneous disease, and all patients do not need the same broad-spectrum antibiotic therapy as complex nosocomial pneumonia.* Curr Opin Infect Dis, 2009. **22**(3): p. 316-25.
53. Niederman, M.S., *Antibiotic treatment of hospital-acquired pneumonia: is it different from ventilator-associated pneumonia?* Curr Opin Crit Care, 2018. **19**(10): p. 0000000000000531.
54. Denys, G.A. and R.F. Relich, *Antibiotic resistance in nosocomial respiratory infections.* Clin Lab Med, 2014. **34**(2): p. 257-70.
55. Ekren, P.K., et al., *Evaluation of the 2016 Infectious Diseases Society of America/American Thoracic Society Guideline Criteria for Risk of Multidrug-Resistant Pathogens in Patients*

with Hospital-acquired and Ventilator-associated Pneumonia in the ICU. Am J Respir Crit Care Med, 2018. **197**(6): p. 826-830.
56. Giuliano, K.K., D. Baker, and B. Quinn, *The epidemiology of nonventilator hospital-acquired pneumonia in the United States.* Am J Infect Control, 2018. **46**(3): p. 322-327.
57. Kohlenberg, A., et al., *Pneumonia associated with invasive and noninvasive ventilation: an analysis of the German nosocomial infection surveillance system database.* Intensive Care Med, 2010. **36**(6): p. 971-8.
58. Schumacher, M., et al., *Hospital-acquired infections--appropriate statistical treatment is urgently needed!* Int J Epidemiol, 2013. **42**(5): p. 1502-8.
59. Lau, B., S.R. Cole, and S.J. Gange, *Competing risk regression models for epidemiologic data.* Am J Epidemiol, 2009. **170**(2): p. 244-56.
60. Austin, P.C. and J.P. Fine, *Practical recommendations for reporting Fine-Gray model analyses for competing risk data.* Stat Med, 2017. **36**(27): p. 4391-4400.
61. Beuscart, J.B., et al., *Overestimation of the probability of death on peritoneal dialysis by the Kaplan-Meier method: advantages of a competing risks approach.* BMC Nephrol, 2012. **13**(31): p. 1471-2369.
62. Andersen, P.K., *Repeated assessment of risk factors in survival analysis.* Stat Methods Med Res, 1992. **1**(3): p. 297-315.
63. Halabi, S., C.C. Wun, and B.R. Davis, *Analysis of survival data with missing measurements of a time-dependent binary covariate.* J Biopharm Stat, 2003. **13**(2): p. 253-70.
64. Giard, M., et al., *Early- and late-onset ventilator-associated pneumonia acquired in the intensive care unit: comparison of risk factors.* J Crit Care, 2008. **23**(1): p. 27-33.
65. Gomez-Zorrilla, S., et al., *Prospective observational study of prior rectal colonization status as a predictor for subsequent development of Pseudomonas aeruginosa clinical infections.* Antimicrob Agents Chemother, 2015. **59**(9): p. 5213-9.
66. Luyt, C.E., et al., *Microbial cause of ICU-acquired pneumonia: hospital-acquired pneumonia versus ventilator-associated pneumonia.* Curr Opin Crit Care, 2018. **20**(10): p. 0000000000000526.
67. Ranzani, O.T., et al., *Invasive and non-invasive diagnostic approaches for microbiological diagnosis of hospital-acquired pneumonia.* Crit Care, 2019. **23**(1): p. 019-2348.
68. Parker, C.M., et al., *Ventilator-associated pneumonia caused by multidrug-resistant organisms or Pseudomonas aeruginosa: prevalence, incidence, risk factors, and outcomes.* J Crit Care, 2008. **23**(1): p. 18-26.
69. Planquette, B., et al., *Pseudomonas aeruginosa ventilator-associated pneumonia. predictive factors of treatment failure.* Am J Respir Crit Care Med, 2013. **188**(1): p. 69-76.
70. Heyland, D.K., et al., *The attributable morbidity and mortality of ventilator-associated pneumonia in the critically ill patient. The Canadian Critical Trials Group.* Am J Respir Crit Care Med, 1999. **159**(4 Pt 1): p. 1249-56.
71. Ibrahim, E.H., et al., *A comparative analysis of patients with early-onset vs late-onset nosocomial pneumonia in the ICU setting.* Chest, 2000. **117**(5): p. 1434-42.
72. Verhamme, K.M., et al., *Pathogens in early-onset and late-onset intensive care unit-acquired pneumonia.* Infect Control Hosp Epidemiol, 2007. **28**(4): p. 389-97.
73. Mosconi, P., et al., *Epidemiology and risk factors of pneumonia in critically ill patients. Intensive Care Unit Group for Infection Control.* Eur J Epidemiol, 1991. **7**(4): p. 320-7.
74. Rello, J., et al., *Variations in etiology of ventilator-associated pneumonia across four treatment sites: implications for antimicrobial prescribing practices.* Am J Respir Crit Care Med, 1999. **160**(2): p. 608-13.
75. Timsit, J.F., et al., *Rationalizing antimicrobial therapy in the ICU: a narrative review.* Intensive Care Med, 2019. **45**(2): p. 172-189.

76. Klompas, M., *Is a ventilator-associated pneumonia rate of zero really possible?* Curr Opin Infect Dis, 2012. **25**(2): p. 176-82.
77. Riaz, O.J., et al., *Bronchoalveolar lavage in the diagnosis of ventilator-associated pneumonia: to quantitate or not, that is the question.* Am Surg, 2011. **77**(3): p. 297-303.
78. Timsit, J.F., et al., *Appropriate endpoints for evaluation of new antibiotic therapies for severe infections: a perspective from COMBACTE's STAT-Net.* Intensive Care Med, 2017. **43**(7): p. 1002-1012.
79. van de Groep, K., et al., *Development and first evaluation of a novel multiplex real-time PCR on whole blood samples for rapid pathogen identification in critically ill patients with sepsis.* Eur J Clin Microbiol Infect Dis, 2018. **37**(7): p. 1333-1344.
80. Ramanan, P., et al., *Syndromic Panel-Based Testing in Clinical Microbiology.* Clin Microbiol Rev, 2017. **31**(1): p. 00024-17.
81. Harbarth, S., et al., *Evaluation of rapid screening and pre-emptive contact isolation for detecting and controlling methicillin-resistant Staphylococcus aureus in critical care: an interventional cohort study.* Crit Care, 2006. **10**(1).
82. Roberts, J.A., et al., *DALI: defining antibiotic levels in intensive care unit patients: are current beta-lactam antibiotic doses sufficient for critically ill patients?* Clin Infect Dis, 2014. **58**(8): p. 1072-83.
83. Bergen, P.J., et al., *Substantial Impact of Altered Pharmacokinetics in Critically Ill Patients on the Antibacterial Effects of Meropenem Evaluated via the Dynamic Hollow-Fiber Infection Model.* Antimicrob Agents Chemother, 2017. **61**(5): p. 02642-16.
84. Roberts, J.A., F.S. Taccone, and J. Lipman, *Understanding PK/PD.* Intensive Care Med, 2016. **42**(11): p. 1797-1800.
85. Pogue, J.M., et al., *Appropriate antimicrobial therapy in the era of multidrug-resistant human pathogens.* Clin Microbiol Infect, 2015. **21**(4): p. 302-12.
86. Zilahi, G., A. Artigas, and I. Martin-Loeches, *What's new in multidrug-resistant pathogens in the ICU?* Ann Intensive Care, 2016. **6**(1): p. 016-0199.
87. Sydnor, E.R. and T.M. Perl, *Hospital epidemiology and infection control in acute-care settings.* Clin Microbiol Rev, 2011. **24**(1): p. 141-73.
88. Santajit, S. and N. Indrawattana, *Mechanisms of Antimicrobial Resistance in ESKAPE Pathogens.* Biomed Res Int, 2016. **2475067**(10): p. 5.
89. Alberti, C., et al., *Epidemiology of sepsis and infection in ICU patients from an international multicentre cohort study.* Intensive Care Med, 2002. **28**(2): p. 108-21.
90. Harris, A.D., et al., *Methodological principles of case-control studies that analyzed risk factors for antibiotic resistance: a systematic review.* Clin Infect Dis, 2001. **32**(7): p. 1055-61.
91. Mazzeffi, M., et al., *Healthcare-Associated Infections in Cardiac Surgery Patients With Prolonged Intensive Care Unit Stay.* Ann Thorac Surg, 2017. **103**(4): p. 1165-1170.
92. van Vught, L.A., et al., *Incidence, Risk Factors, and Attributable Mortality of Secondary Infections in the Intensive Care Unit After Admission for Sepsis.* Jama, 2016. **315**(14): p. 1469-79.
93. Kao, K.C., et al., *Risk Factors of Methicillin-Resistant Staphylococcus aureus Infection and Correlation With Nasal Colonization Based on Molecular Genotyping in Medical Intensive Care Units: A Prospective Observational Study.* Medicine, 2015. **94**(28): p. 0000000000001100.
94. Ziakas, P.D., T. Anagnostou, and E. Mylonakis, *The prevalence and significance of methicillin-resistant Staphylococcus aureus colonization at admission in the general ICU Setting: a meta-analysis of published studies.* Crit Care Med, 2014. **42**(2): p. 433-44.
95. Detsis, M., S. Karanika, and E. Mylonakis, *ICU Acquisition Rate, Risk Factors, and Clinical Significance of Digestive Tract Colonization With Extended-Spectrum Beta-Lactamase-*

Producing Enterobacteriaceae: A Systematic Review and Meta-Analysis. Crit Care Med, 2017. **45**(4): p. 705-714.
96. Raman, G., et al., *Risk factors for hospitalized patients with resistant or multidrug-resistant Pseudomonas aeruginosa infections: a systematic review and meta-analysis.* Antimicrob Resist Infect Control, 2018. **7**(79): p. 018-0370.
97. Zahar, J.R., et al., *Screening for Intestinal Carriage of Extended-spectrum Beta-lactamase-producing Enterobacteriaceae in Critically Ill Patients: Expected Benefits and Evidence-based Controversies.* Clin Infect Dis, 2019. **68**(12): p. 2125-2130.
98. Tabah, A., et al., *Characteristics and determinants of outcome of hospital-acquired bloodstream infections in intensive care units: the EUROBACT International Cohort Study.* Intensive Care Med, 2012. **38**(12): p. 1930-45.
99. Burnham, J.P., M.A. Lane, and M.H. Kollef, *Impact of Sepsis Classification and Multidrug-Resistance Status on Outcome Among Patients Treated With Appropriate Therapy.* Crit Care Med, 2015. **43**(8): p. 1580-6.
100. von Cube, M.K., et al., *Relative risk and population-attributable fraction of ICU death caused by susceptible and resistant Pseudomonas aeruginosa ventilator-associated pneumonia: a competing risks approach to investigate the OUTCOMEREA database*: Intensive Care Med. 2018 Jul;44(7):1177-1179. doi: 10.1007/s00134-018-5109-9. Epub 2018 Mar 16.