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Ecole doctorale Biologie et santé

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Thèse :

Pour obtenir le grade de
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Discipline : Epidémiologie et santé publique

Présentée et soutenue publiquement

Par

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TITRE :

Estimation de la mortalité attribuable aux infections nosocomiales en réanimation. Prise en compte de l'évolution de la gravité des patients en réanimation.

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Résumé en Français :
La mesure du sur-risque de décès liés à une infection nosocomiale est gênée par la diversité des définitions utilisées, la présence de nombreux facteurs confondant et risques en compétition. Nous avons développé les données de la littérature concernant le sur-risque de décès lié aux pneumonies nosocomiales en réanimation. Nous avons montré, la diversité des estimations retrouvées et énuméré les causes probables des divergences. Notre recherche a porté sur la prise en compte de la gravité et de l'évolution initiale des malades comme facteur de confusion dans l'analyse de la relation entre infection nosocomiale et mortalité. Nous avons montré que, indépendamment des scores de gravité à l'admission, les patients qui évoluent le plus mal ont un risque accru d'infection nosocomiale et bien-sûr de décès. Dans le but d'ajuster sur l'évolution de la gravité en cours de séjour, nous avons validé les scores de dysfonction d'organes LOD et SOFA en cours de séjour. Nous avons crée un score de gravité baptisé TRIO basé sur la gravité à l'admission et l'évolution au cours des 3 premiers jours de réanimation et donc particulièrement adapté à la population exposée au risque d'infection nosocomiale Dans un deuxième temps, nous avons utilisé ces outils dans différentes applications avec différentes méthodologies statistiques (étude exposés-non exposés appariés avec analyse par régression logistique conditionnelle ou modèle de Cox marginal, étude de cohorte avec utilisation de modèles de Cox avec covariables dépendantes du temps). Enfin, à partir de ces résultats, nous avons exposé brièvement quels pourraient être les développements statistiques utilisables pour améliorer la précision de l'estimation du sur-risque de mortalité associée aux infections nosocomiales.

Titre en anglais : Estimation of attributable mortality associated with ICU-acquired nosocomial infection with special emphasis on evolution of severity in ICU.

Résumé en anglais :
The estimation of the over-risk of death associated with nosocomial infection is difficult because of the inaccuracy of the definition used, a numerous of confounding factors and competing events. We discussed data available in the literature concerning the over-risk of death associated with ICU-acquired nosocomial pneumonia. We have shown that the risk estimation is highly variable and described the reasons for such variability. The target of our work was to take into account the severity on admission and the evolution of the severity as confounding factor of the relationship between nosocomial infection and death. We have shown that, independently of severity scores on admission, patients with the worst evolution have an increased risk of nosocomial infection and of mortality. In an attempt to adjust on these confounding factors we validate the accuracy of LOD and SOFA scores measured during the ICU stay. We also built a new score named TRIO based on severity on admission and evolution of the severity during the first 3 days particularly adapted to the population exposed to nosocomial infections. We used these tools in various examples using various statistical methods (exposed-unexposed studies with marginal Cox model with time-dependent covariates or conditional logistic regression). Finally, we briefly described the statistical tools able to improve the measurement of the risk estimations.

Discipline: Epidémiologie et santé publique

Mots clés : cox, régression logistique conditionnelle, risque compétitif, pneumonie nosocomiale, réanimation, infection, facteur confondant, mortalité attribuable.

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A Céline, qui me supporte...

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Remember how much you don't know

William Osler

L'observation scientifique est toujours une observation polémique

Gaston Bachelard

Half of the medicine today is wrong but we don't know which half

New York Times March 16,2003

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Articles se rapportant à la thèse:

1-Timsit JF, Fosse JP, Troché G, De lassence A, Alberti C, Garrouste-Orgeas M, Azoulay E, Chevret S, Moine P, Cohen Y - Accuracy of a composite score using daily SAPSII and LOD scores for predicting hospital mortality in ICU patients hospitalized for more than 72 hours- Intens Care med 2001; 27:1012-1021

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Introduction : Intérêt de l'estimation de la mortalité induite par les infections nosocomiales ?

L'estimation du retentissement des événements iatrogènes survenant chez les malades de réanimation sur leur pronostic représente l'un des objectifs de la recherche épidémiologique en réanimation.

Cette estimation apparaît nécessaire pour mieux évaluer les actions de prévention à mettre en œuvre et pour orienter les priorités de recherche [1].

Actuellement, l'hôpital se transforme. Il est devenu nécessaire d'évaluer la qualité des soins que nous prodiguons afin de les améliorer.

L'infection nosocomiale en réanimation est l'un des paramètres potentiels qui permettraient de mesurer la qualité des soins. Il est devenu ainsi obligatoire de surveiller les infections nosocomiales en France (Décret n°88-657 du 6 mai 1988 (JO du 8 mai 1988), Circulaire n°263 du 13 octobre 1988 (BO 88/45), Circulaire Direction Générale de la Santé (DGS)/VS/VS2 - DH/E01 n° 17 du 19 avril 1995 (Bulletin Epidémiologique Hebdomadaire (BEH) n° 28, 1995). L'Agence Nationale d'Accréditation et d'Evaluation en Santé (ANAES) a très rapidement décidé d'intégrer ce type d'indicateurs dans son référentiel (Manuel d'accréditation de l'ANAES : Qualité et prévention, Février 1999).

Cependant, son utilisation en réanimation comme indicateur de résultats est loin d'être simple. En effet, afin d'être un bon indicateur, plusieurs conditions doivent être réunies :

(1) L'événement doit être fréquent et entraîner une morbidité et une mortalité importantes. Cependant, nombreux sont les travaux contradictoires concernant la mortalité et la morbidité attribuables à l'infection nosocomiale en réanimation. Il semble, en effet, que l'infection nosocomiale en réanimation soit la plus fréquente chez les patients les plus graves (EPIC

study par exemple [2]). Il devient donc difficile de décider si les patients les plus graves décèdent avec une infection nosocomiale ou du fait d'une infection nosocomiale

(2) L'événement doit être facile à détecter, de diagnostic aisé et reproductible

(3) La surveillance de cet événement doit être simple

(4) Cet événement doit être évitable[3].

Les responsables du Comité Technique national des Infections Nosocomiales (CTIN) ont, pour l'instant, décidé de ne pas recommander l'utilisation de ce type de marqueur de qualité en réanimation car les points 1, 2, (3) et 4 restent très discutés.

Nous avons centré notre travail de recherche sur la relation qui existe entre l'infection nosocomiale et la mortalité des patients de réanimation.

Dans une première partie, nous avons rappelé et discuté l'estimation des sur-risques de décès et du risque attribuable.

Dans une deuxième partie, nous avons développé les données de la littérature concernant le sur-risque de décès lié aux pneumonies nosocomiales en réanimation. Nous avons montré, à partir des données de la littérature, la diversité des estimations retrouvées et énuméré les causes probables des divergences.

Dans une dernière partie, nous avons résumé les développements réalisés pendant la thèse qui ont essentiellement concerné la prise en compte des facteurs de confusion dans l'analyse de la relation entre infection nosocomiale et mortalité. Dans un premier temps, nous avons développé des outils permettant la comparabilité de la gravité des sous groupes de patients exposés au risque de pneumonie nosocomiale. Dans un deuxième temps, nous avons utilisé ces outils dans différentes applications avec différentes méthodologies statistiques (étude exposés-non exposés appariés avec analyse par régression logistique conditionnelle ou modèle de Cox marginal, étude de cohorte avec utilisation de modèles de Cox avec

covariables dépendant du temps). Enfin, à partir de ces résultats, nous avons exposé brièvement quels pourraient être les développements statistiques utilisables pour améliorer la précision de l'estimation du sur-risque de mortalité associée aux infections nosocomiales.

I Mortalité attribuable : Définitions, Principe d'estimation

1.1 Définitions [4, 5]

1) Risque attribuable

Le « risque attribuable » est une mesure qui permet d'évaluer les conséquences en termes de santé publique d'une association entre un facteur d'exposition et une maladie. Il est défini comme la proportion de malades qui peut être attribué à l'exposition, et s'écrit formellement comme

$$RA = \frac{P(M) - P(M|\overline{E})}{P(M)} \qquad (1)$$

où $P(M)$ est la probabilité de maladie dans la population, et $P(M|\overline{E})$ est la probabilité de maladie théorique dans la même population après suppression de l'exposition. Le risque attribuable prend en compte non seulement la force d'association entre l'exposition et la maladie, mais aussi la prévalence de l'exposition dans la population. En effet, on peut appliquer le théorème de Bayes à (1) et obtenir :

$$RA = \frac{P(E)(RR-1)}{1+P(E)(RR-1)} \qquad (2)$$

c'est à dire une fonction de la prévalence de l'exposition, $P(E)$, et du risque relatif, $RR = \frac{P(M|E)}{P(M|\overline{E})}$.

2) Mortalité attribuable

Le concept de mortalité attribuable est défini comme le risque attribuable, quand le décès se substitue à la maladie. Elle est donc définie comme la proportion de décès qui puissent être attribués à une exposition donnée :

$$MA = \frac{P(D) - P(D|\overline{E})}{P(D)} \qquad (3)$$

où $P(D)$ est la probabilité de décès dans la population, et $P(D|\overline{E})$ est la probabilité de décès théorique dans la même population après suppression de l'exposition. Dans un contexte de mortalité, le facteur d'exposition est en règle dit « facteur pronostique ».

La mortalité attribuable est souvent interprétée comme la proportion de décès qui puissent être supprimés si le facteur d'exposition était totalement supprimé de la population. Cette interprétation doit cependant être prudente, car 3 conditions doivent être réunies pour sa validité :

- l'estimation doit être non biaisée (voir section 1.2)
- le facteur d'exposition doit être causal et non seulement associé au décès
- la suppression de l'exposition ne doit pas modifier la distribution d'autres facteurs pronostiques.

1.2 Estimation

La mortalité attribuable peut être estimée à partir des divers types d'études cliniques :

- études de cohorte
- études transversales
- études cas-témoins

En effet, toutes les quantités intervenant dans l'équation (3) peuvent être estimées à partir de ces études, sauf pour les études cas-témoins, pour lesquelles on ne peut qu'appliquer l'équation (2) et estimer $P(E)$ à partir de la proportion des sujets vivants qui avaient le facteur pronostique étudié, en supposant de plus que le décès est rare, justifiant l'estimation du risque relatif par un odds ratio (OR). Autrement, on peut aussi écrire d'après l'équation (3) :

$$MA = \frac{P(E|D)(RR-1)}{RR} \qquad (4)$$

et estimer directement la quantité $P(E|D)$ à partir des individus décédés, et le risque relatif (RR) à partir de l'odds ratio.

Enfin, il faut que l'échantillon de population dans lequel est conduit l'étude de cohorte soit strictement représentatif de la population globale. Cette condition peut être difficile à réaliser et à vérifier par exemple en réanimation ou la catégorie de malade admis varie d'un service à l'autre, d'un hôpital à l'autre et même d'un pays à l'autre. La prévalence de l'exposition, dans ces conditions, peut être différente d'une cohorte à une autre, conduisant à des difficultés de généralisation (5).

1) Estimation non ajustée

A partir des trois types d'études considérées précédemment, il est simple d'obtenir une estimation non ajustée (« brute ») de la mortalité attribuable, en appliquant les équations soit (3), soit (4). Une estimation de la variance peu être obtenue par la delta-méthode, ce qui permet alors d'obtenir un intervalle de confiance pour la mortalité attribuable, en supposant la normalité asymptotique de MA (bien que d'autres méthodes aient été proposées).

Les estimateurs non ajustés de la mortalité attribuable sont en général biaisés, car ils omettent de prendre en compte d'autres facteurs pronostiques, facteurs de confusion dans la mesure de l'association entre le facteur étudié et la mortalité. Ainsi, si on veut estimer la mortalité attribuable au facteur X_1, en présence d'un autre facteur X_2, l'estimation non ajustée n'est valide que si au moins une des deux conditions suivantes est satisfaite :

- X_1 et X_2 sont distribués de façon indépendante dans la population
- L'exposition au facteur X_2 n'augmente pas, à elle seule, le risque de décès (X_2 n'est pas un facteur pronostique).

2) Estimation ajustée

Différentes approches statistiques ont été proposées pour calculer un estimateur ajusté non biaisé de la mortalité attribuable.

- ***Méthode de Mantel-Haenszel***

Cette approche permet l'ajustement sur un (ou plus de un) facteur qualitatif à plusieurs classes, définissant J strates différentes au sein de la population.

Elle est basée sur la formulation de la mortalité attribuable comme une fonction du risque relatif (ou de l'odds ratio dans une étude cas-témoin) et de la prévalence de l'exposition chez les individus décédés, comme formulée dans l'équation (4).

Si l'estimation ponctuelle est simple, l'estimation de la variance est plus complexe.

L'hypothèse sous jacente à cette approche est l'existence d'un risque relatif (odds ratio) commun ou homogène entre les strates, qui conduit à une absence d'interaction entre les

facteurs d'ajustement et le facteur pronostique étudié. S'il existe une telle interaction, l'estimateur de Mantel-Haenszel est biaisé.

- ***Méthode de la somme pondérée***

Cette approche permet l'ajustement sur un (ou plus de un) facteur qualitatif à plusieurs classes, définissant J strates différentes au sein de la population. Elle consiste à écrire la mortalité attribuable comme une somme pondérée sur les diverses strates :

$$MA = \sum_j w_j MA_j \qquad (5)$$

où MA_j et w_j sont respectivement les mortalités attribuables spécifiques de la strate j et la pondération correspondante. Différents indices de pondération ont été discutés, depuis la prévalence de sujets décédés dans la strate j, ou l'inverse de la variance de MA sur la strate j rapportée à la somme sur l'ensemble des strates.

Cette approche ne fait pas d'hypothèse de RR (ou OR) commun. En effet, les RR (ou OR) sont estimés séparément dans chaque strate, permettant de tenir compte d'une éventuelle interaction.

Sa principale limite réside dans un biais sur petits échantillons.

- ***Estimation ajustée basée sur un modèle de régression***

Cette approche a été proposée initialement par Bruzzi et al (6). En exprimant la mortalité attribuable de la façon suivante :

$$MA = 1 - \sum_j \sum_i \rho_{ij} / RR_{i|j} \qquad (6)$$

c'est à dire comme une somme sur les strates j des facteurs d'ajustement et sur tous les niveaux d'exposition (en règle, simplement deux, présence et absence du facteur pronostique). La quantité ρ_{ij} représente la proportion de sujets décédés qui avaient le niveau d'exposition i et la strate d'ajustement j, et $RR_{i|j}$ représente le risque relatif de décès pour le niveau d'exposition i dans la strate d'ajustement j.

Ce modèle est très général [6]. Il s'applique à tous les types d'études à partir desquelles on peut estimer ρ_{ij} à partir des proportions observées correspondantes, et estimer $RR_{i|j}$ à partir des coefficients estimés par la méthode du maximum de vraisemblance dans un modèle de régression (qu'il s'agisse d'un modèle de régression logistique – conditionnel ou non – ou d'un modèle de régression de Poisson). Il permet de tester des hypothèses et sélectionner les modèles (notamment par l'introduction de termes d'interaction). Enfin, il généralise les approches ajustées et non ajustées.

L'estimation de la variance est plus complexe, car elle doit tenir compte de la corrélation entre les ρ_{ij} et les $RR_{i|j}$.

1-3 Mortalité attribuable: Mesures effectuées en réanimation

Mortalité attribuable dans les revues de réanimation.

Une étude de cohorte portant sur 1144 malades ventilés plus de 48 heures a recherché la mortalité attribuable à la pneumonie nosocomiale [7]. Une analyse exposés non exposés à été effectuée sur 135 patients ventilés avec une pneumonie et 135 patients témoins ayant la même indication à la ventilation mécanique, le même statut immunologique et cardiaque, le même âge, la même probabilité de décès prédite (par le score SAPS II) à l'admission et le même score de Glasgow à l'admission. Le taux brut de mortalité des patients ayant présenté une pneumonie était de 41%, alors qu'il n'était que de 14% chez les témoins appariés. La

mortalité attribuable a été estimée à 27%, soit la différence entre ces deux taux qui définit une estimation, non pas de la mortalité attribuable, mais de $P(D|E)-P(D|\bar{E})$. La mesure effectuée est celle de la mortalité attribuable chez les exposés

En fait, connaissant l'incidence de la pneumonie nosocomiale dans la cohorte suivie (141 patients, 12.3%), la proportion de décès attribuable dans la population P(D) – P(D|non E) et plus que de 19.2%.

Ainsi, malgré des titres évoquant la mesure d'un risque attribuable (ici, « *Mortality rate attributable to ventilator-associated nosocomial pneumonia in an adult intensive care unit : a prospective case-control study* »), deux définitions distinctes sont donc confondues, la mortalité attribuable chez les exposés (ici 27%) et la mortalité attribuable dans la population (dans cet exemple 19.2%).

Enfin, les études publiées en réanimation mesurent en règle un sur-risque de décès grâce à des modèles multiplicatifs et non un risque attribuable. C'est plutôt la variabilité des estimations de ce sur-risque de décès qui va être étudiée dans les pages suivantes.

1-4 Effet de l'erreur de mesure de l'exposition sur le sur-risque de décès

En supposant que les méthodes diagnostiques soient sans erreurs, la prévalence vraie de la maladie est disponible.

En fait l'estimation de la prévalence de la maladie dépend de l'erreur de mesure du test diagnostic.

On montre que :

$$Per=\frac{FP+VP}{M+M_0}=((Se+Sp-1)Pe)+(1-Sp)$$

FP : Faux positifs, VP : Vrais positifs,

Per estimation de la prévalence en présence d'une erreur,

Pe : prévalence vraie.

On surestime les prévalences faibles en présence d'une erreur ce d'autant que la spécificité est faible.

Si la pneumonie survient chez 10% des malades, et que l'on utilise un test avec une sensibilité Se de 90% et une spécificité Sp de 80% (chiffre parfaitement plausible concerant les tests utilisés pour faire le diagnostic de pneumonie nosocomiale, voir plus loin) la prévalence mesurée sera de 27%!!. Cette surestimation de la prévalence conduira à une sousestimation obligatoire du sur-risque de décès associé à cette pathologie[8].

II- Estimation de la mortalité attribuable aux infections nosocomiales en réanimation : l'exemple de la pneumonie

II-1 Risque de décès attribuable à la pneumonie nosocomiale, résultats obtenus dans la littérature

La mortalité des patients atteints de pneumonie nosocomiale acquise sous ventilation mécanique (VAP) est élevée : de 25 % à 76 % selon les séries [9].

De nombreux paramètres influencent le pronostic de ces patients [10-15]. De nombreux facteurs sont liés au terrain sous-jacent : âge, immunodépression, présence d'une maladie chronique grave et la gravité. Le facteur pronostique le plus fréquemment retrouvé est la sévérité de la maladie aiguë telle qu'elle est évaluée par les scores de gravité généraux (SAPS II, Apache II ou III, MPMo) mesurés à l'admission [16] ou même après 3 jours de séjour en réanimation (MPM72 [15]). Les patients qui ne s'améliorent pas en réanimation ont un risque plus élevé de présenter une pneumonie et de mourir [17].

De nombreuses études ont essayé de répondre à la question : est-ce que la pneumonie nosocomiale, de son seul fait, augmente le risque de décès chez le malade de réanimation ?

La plupart des auteurs retrouvent un sur-risque de décès associé à l'acquisition des pneumonies nosocomiales. Cependant, d'autres auteurs retrouvent des résultats opposés et en

particulier aucune différence de mortalité entre les patients ayant présenté une pneumonie et les autres [13, 18-21] (Tableau 1).

Tableau 1 : Estimations de la « mortalité attribuable » à la pneumonie nosocomiale retrouvées dans la littérature à partir d'études exposés-non exposés dans une cohorte

Référence	Méthodes diagnostiques	Nombre de pneumonies	Type de patients	Mortalité pneumonie	Mortalité contrôles	OR (IC95%)	Mortalité attribuable	Nombre témoins :nombre de pneumonies Critères d'appariement
Cunnion 1996 [22]	clinique	20	Chir.	55%	5%	23.2 (NA), p<0.002	50%	2 :1 Unité durée de séjour>48 heures
Cunnion 1996 [22]	clinique	20	Med	55%	7.5%	15.1 (NA) p<0.002	47.5%	2 :1 Unité, Durée de séjour>4_ heures
Fagon 1993 [23]	Brosse + LBA	48	ventilés	54.2 %	27.1%	2.0 (1.61-2.49)	27.1% (8.3-45.9)	1 :1 age, SAPS, symptôme principal, date, durée de VM
Baker 1996 [13]	Brosse + LBA	62	Trauma	24%	24%	1.0	0%	Age, sexe, score de gravité, nombre de diagnostic à la sortie
Heyland 1999 [18]	Brosse+LBA	173	Polyvalente multicentrique	23.7 %	17.9%	1.3 (p>0.05)	5.8% (-2,4- 14)	1:1 med/chir apache II , durée de d'exposition
Craig 1984 [24]		54	polyvalente	20.4%	5.6%	3.6 (p<0.001)	14.8 % (?)	1 :1 Age, sexe, diagnostic, facteur de risque, intervention chirurgicale
Bercault 2001 [7]	Brosse	135	Ventilés	41	14	2.7 (1.8-3.1) (régression logistique) 2.1 (1.2-3.6) (modèle de Cox)	27% (?)	1 :1 Age, immunodépression, Cause d'admission, score de Glasgow, durée d'exposition au risque
Papazian 1996 [20]	Brosse	85	Ventilés	40	38.8	1.3 (p>0.05)	1.2% (?)	1 :1 diagnostic indication de la ventilation mécanique, age sexe, score apache, durée d'exposition

Une seule étude cas-témoin appariée a été publiée [25]. Elle concerne 108 patients décédés (cas) qui ont été comparés à 108 patients vivants (témoins) appariés (mêmes âge, même gravité : score APACHE II, et même durée d'exposition au risque). Le nombre de patients ayant présenté une pneumopathie était strictement identique entre les vivants et les morts (39 patients : 36.1%).

Dans cette étude, le nombre de patients avec un traitement corticoïde était différent entre les vivants et les morts. Les facteurs de risque d'acquisition d'une pneumonie en analyse de régression logistique montrait que l'utilisation d'une antibiothérapie était associée au risque de pneumonie (OR : 2.69 (IC 95%:1.44-5.03)).

II-2 Causes potentielles des divergences retrouvées dans la littérature

II-2-1 Définition des pneumonies nosocomiales : variable et non consensuelle

Malgré de nombreuses tentatives de consensus internationaux sur le diagnostic des pneumonies nosocomiales, les définitions ne sont pas toutes les mêmes en fonction des pays, des régions et même des unités de soins.

Les discordances tiennent à la méthode du diagnostic bactériologique (allant des prélèvements proximaux qualitatifs sensibles et peu spécifiques aux prélèvements quantitatifs distaux sous fibroscopie plus spécifiques mais probablement moins sensibles).

Le type de prélèvement utilisé explique des variations d'incidence de l'exposition très importantes (Tableau 2).

Tableau 2 : Estimations rapportées dans la littérature des incidences de pneumonie nosocomiales

Auteurs	Nb patients	Critères diagnostiques	Incidence	Mortalité
Réanimation				
Salata 87 [26]	51	Clinique-autopsie	41	76
Craven 86 [27]	233	clinique	21	55
Langer 89 [28]	724	clinique	23	44
Fagon 89 [29]	567	Brosse	9	71
Kerver 87 [30]	39	clinique	67	30
Driks 87 [31]	130	clinique	18	56
Torres 90 [32]	322	Clinique+brosse	24	33
Baker 96 [13]	514	Brosse/LBA	5	24
Kollef 93 [33]	277	Clinique	16	37
Fagon 96 [34]	1118	Brosse LBA	28	53
Timsit 96 [35]	387	Brosse LBA	15	57
Cook 98 [11]	1014	Clinique + brosse	18	24
Tejada Artigas 2001 [36]	103	LBA Brosse	22	44
SDRA				
Sutherland 95 [37]	105	Brosse LBA	15	38
Delclaux 97 [38]	30	PDP LBA	60	63
Chastre 98 [39]	56	Brosse LBA	55	78
Meduri 98 [40]	94	Brosse LBA	43	52
Markowicz 2000 [41]	134	Brosse LBA	37	57

Par exemple, dans la série de Cook et coll [42], 3 définitions de pneumonies nosocomiales acquises sous ventilation mécanique ont été utilisées. Dans cette étude, 800 patients ont été randomisés pour recevoir du sucralfate ou de la ranitidine en prophylaxie de l'ulcère de stress.

- Pneumonie clinique : infiltrat radiologique nouveau, et au moins 2 des signes suivants : température >38°5 ou <36°5, hyperleucocytose > 10 000/mm^3 ou leucopénie < 3 000/mm^3, aspiration purulente, micro-organisme(s) isolé dans l'aspiration trachéale.
- Pneumonie probable : pneumonie clinique et brosse de Wimberley > 10^3 CFU/ml ou culture du LBA > 10^4 cfu/ml ou liquide pleural positif ou histologie pulmonaire retrouvant une pneumonie histologique ou un abcès.
- Pneumonie certaine : abcès radiologique ou histologique avec bactériologie positive du tissu pulmonaire ou d'une ponction à l'aiguille.

En fonction de la définition, l'incidence des pneumonies nosocomiales variait de plus de 20% à moins de 1% (figure 1).

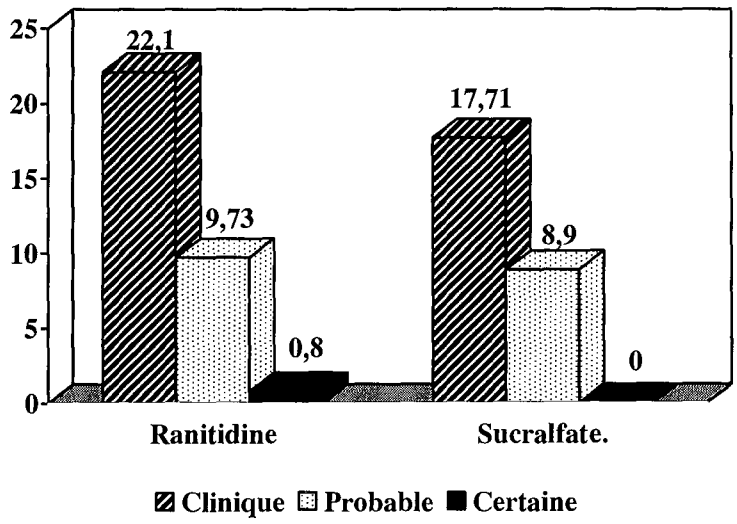


Figure 1 : Estimation de l'incidence de la pneumonie nosocomiale en fonction de la définition (d'après Cook et al, [41])

Le risque relatif de pneumonie nosocomiale et surtout la fraction de risque attribuable au type de prophylaxie utilisée variait ainsi de façon considérable (tableau 3).

Tableau 3 : Influence de la définition (clinique, probable, certaine) sur l'estimation du risque relatif (RR) et du risque attribuable (RA) de la pneumopathie nosocomiale (d'après Cook et al, [41])

Critères	Ranitidine N Pn/ N Pat	Sucralfate N Pn/N Pat	RR (IC 95%)	RA (IC 95%) %	P
Clinique	132/596	107/604	1.25 (0.95-1.57)	4.4 (-0.1-9.0)	0.06
Probable	58/596	54/604	1.09 (0.77-1.55)	0.8 (-2.5-4.1)	0.64
Certaine	5/596	0/604	Non défini	0.8 (0.1-1.6)	0.03

De même, dans les réseaux nationaux de surveillance des infections nosocomiales, les définitions ne sont pas consensuelles [43] (tableau 4).

Tableau 4 : Discordances des définitions d'infections nosocomiales en réanimation dans 6 réseaux européens

Nom du réseau	NSIH-ICU	REA-SE	PREZIES-ICU	ENVIN-UCI	KISS-ICU	NNIS (CDC)
Pays	Belgique	France	Pays Bas	Espagne	Allemagne	Etats-unis
Patients inclus	*> 48 heures de séjour*	*> 48 heures de séjour*	*> 48 heures de séjour*	*> 24 heures de séjour*	*tous*	*tous*
Définition d'une acquisition	*Plus de 2 jours après l'entrée*	*Plus de 2 jours après l'entrée*	*Non présent à l'admission*	*Non en incubation à l'admission*	*Non en incubation à l'admission*	*Non en incubation à l'admission*
Diagnostic	*Clinique*	*Clinique + prélèvements distaux*	*Clinique*	*Clinique*	*Clinique*	*Clinique*
Quelle infection ?	*Uniquement la première*	*Uniquement la première*	*Toutes*	*Toutes*	*Toutes*	*Toutes*

Enfin, en France, au travers d'un questionnaire envoyé à l'ensemble des réanimateurs (enquête NOSOREF), nous avons retrouvé une grande variabilité des méthodes utilisées. Pour utiliser l'infection nosocomiale comme marqueur de qualité, il faut en effet connaître la manière dont elle est recueillie et analysée en routine en France. Il est très probable que la manière de la diagnostiquer (constitution du numérateur) et la manière de la rapporter à un dénominateur soient variables d'un endroit à l'autre.

Trois réflexions sont à la base de cette étude : (1) Les définitions proposées ne sont pas toujours adaptées à la pratique quotidienne de chacun ; (2) La façon dont le diagnostic des infections nosocomiales est fait n'est pas toujours homogène et (3) Le dénominateur utilisé et utilisable est variable en fonction des unités. Cette enquête n'a pas pour but de proposer une définition applicable par tous mais plutôt de connaître les pratiques, et d'identifier les différents schémas de surveillance utilisés en France.

Au total, 480 questionnaires ont été adressés à l'ensemble des centres de réanimation français (double envoi postal). Deux cent cinquante (52%) questionnaires écrits sont évaluables. Un échantillon aléatoire de 150 des 230 non répondeurs a été interrogé par téléphone à l'aide d'un questionnaire simplifié. Une analyse descriptive des résultats concernant l'organisation de la surveillance, le dépistage de la colonisation à germe multirésistant et le diagnostic d'infection nosocomiale a été réalisée. Une tentative de réduction du nombre de variables grâce à une analyse factorielle des correspondances est en cours.

L'objectif final est de décrire les pratiques en France, de définir un petit nombre de questions simples qui résument les pratiques de routine et les attitudes des médecins réanimateurs. Les prélèvements bactériologiques sont réalisés après mise en route d'une antibiothérapie probabiliste à large spectre jamais (28% des centres), rarement (40%), parfois (17%) souvent (15%). Ce résultat peut avoir des conséquences importantes dans l'évaluation de l'incidence

de la maladie car une antibiothérapie probabiliste peut négativer les prélèvements bactériologiques [44].

L'utilisation des méthodes diagnostiques était variable d'un centre à l'autre et variable en fonction des régions C-Clin en France [45]. Ainsi, les techniques les plus spécifiques (direct du lavage alvéolaire avec pourcentage de cellules infectées) ne sont réalisées que par le quart des réanimations. A l'opposé, l'aspiration trachéale qualitative (technique sensible mais peu spécifique) est utilisée seule pour le diagnostic des pneumonies nosocomiales dans 30% des centres. En analyse factorielle des correspondances, l'essentiel de la variabilité des pratiques est lié au type d'établissement de soins (prélèvements distaux plus fréquents dans les structures hospitalo-universitaires).

II-2-2 La gravité des épisodes de pneumonies nosocomiales est variable en fonction de paramètres liés au malade et liés à la pneumonie

Facteurs liés à l'hôte (tableau 5)

La maladie sous-jacente : l'âge, l'immunodépression, l'état antérieur (mesuré par le score de Mc Cabe), sont des facteurs de risque retrouvés dans la littérature.

La cause d'admission en réanimation modifie aussi la mortalité des pneumonies nosocomiales, les patients porteurs d'une pneumonie ayant un pronostic plus défavorable s'ils sont admis après une chirurgie non programmée [18, 19]ou si ce sont des malades de réanimation médicale [20, 23]. Par ailleurs, chez les patients de chirurgie cardiaque [18] et les patients traumatisés [13, 46], la mortalité associée à la survenue d'une pneumonie nosocomiale apparaît moindre.

Un autre élément qui décrit bien la population d'étude est la cause de la ventilation mécanique. Ainsi, certains auteurs mentionnent une proportion plus importante de décès

d'infection nosocomiale chez les patients ventilés pour une maladie neuro-musculaire que chez les patients ventilés pour un choc cardiogénique [28].

Les patients présentant un syndrome de détresse respiratoire aiguë de l'adulte (SDRA) ont, eux-aussi, un risque plus important de pneumonie nosocomiale et de mortalité [28, 37-41]. Il est généralement admis que l'infection nosocomiale, la pneumonie en particulier, est une cause fréquente de décès dans ces circonstances.

Le rôle de la maladie sous-jacente dans le sur-risque de décès associé à la pneumonie nosocomiale doit être aussi considéré. Certains patients sont si sévères qu'un sur-risque de décès est très difficile à mettre en évidence. A l'opposé, les patients les moins sévères ont une immunité respectée qui permet une réponse adéquate de l'hôte à l'agression bactérienne et donc un moindre sur-risque de décès. C'est pour les patients de gravité intermédiaire que le sur-risque potentiel de décès est le plus probable [47].

Tableau 5 : Facteurs endogènes influençant la mortalité des pneumonies nosocomiales sous ventilation mécanique

Maladie sous jacente
Maladie rapidement fatale
Age>60 ans
Immunodépression
Chirurgie (non cardiaque)
Gravité de la maladie aiguë
SAPS
APACHE II
Transfert d'une autre unité de court séjour
Gravité au moment de la pneumonie
SAPS
Température
Lymphocytes
Dysfonctions d'organes
Etat de choc
Aggravation respiratoire
Infiltrats bilatéraux
Intubation
Antibiothérapie préalable

Sévérité de la pneumonie

Plusieurs études ont montré que la gravité des patients (telle que mesurée par les scores de gravité [16, 35, 48], les scores de dysfonction d'organes [35], la présence d'un choc [16], l'intensité de l'activation de la cascade inflammatoire [12, 49]) le jour de la pneumonie était associée à la mortalité de ces patients. Ces éléments suggèrent qu'il est nécessaire d'utiliser la gravité comme paramètre d'appariement ou d'ajustement lorsque l'on cherche à estimer la mortalité des pneumonies nosocomiales. L'importance de ce facteur de confusion et la difficulté à la mesurer sera développée plus loin.

Germes en cause

Il existe certainement des différences de mortalité en fonction du germe responsable de la pneumonie. Ainsi, les germes comme *Haemophilus influenzae* ou *Streptococcus ssp* ne sont pas associés à un sur-risque de décès [50].

A l'opposé, dans l'étude exposés-non exposés de Fagon et al [51]ou dans l'étude de cohorte de Kollef et coll [33], *Pseudomonas* sp. et *Acinetobacter baumanni* était les germes présents dans les pneumonies associés avec le plus grand sur-risque de décès estimé. Cependant, bien qu'il soit difficile d'estimer les facteurs de virulence des micro-organismes, des germes comme *A. baumanni* ont peu de facteurs de virulence et ont été longtemps considérés comme des germes commensaux. Les pneumonies à ce type de germes surviennent le plus souvent tardivement pendant le séjour chez des patients pour lesquels le statut immunitaire est plus profondément altéré.

Le Staphylocoque doré résistant à la méticilline (SDMR) est, lui aussi, associé à une mortalité plus élevée que le staphylocoque doré sensible (SDMS) [52]. Cependant, les patients qui présentent une pneumonie à SDMR sont plus âgés, ont plus souvent de maladies sous-jacentes [52], ont reçu plus souvent des antibiotiques, ont plus souvent un

cathéter central, et sont hospitalisés depuis plus longtemps [53]. De plus, aucune étude expérimentale n'a pu mettre en évidence de facteurs de virulence particuliers liés à la méticillino-résistance.

On peut d'autant plus s'interroger sur le sur-risque de décès induit par la méticillino-résistance que ce résultat peut être expliqué par des variables confondantes. En effet, la vancomycine, traitement de référence des SDMR, diffuse beaucoup moins bien et a une activité moindre que la méticilline, traitement de référence des SDMS. Ainsi, le sur-risque de décès retrouvé pour certains germes pourrait être, en partie, lié à une moindre efficacité des antibiotiques disponibles.

Antibiothérapie instituée

Trois types d'antibiothérapie inefficace sont définis dans la littérature, (1) l'antibiothérapie inadéquate (l'antibiotique utilisé n'est pas actif *in vitro* sur le germe retrouvé) et (2) l'antibiothérapie inadaptée (malgré une dose et une adéquation correcte, le patient s'aggrave sous traitement). Enfin (3) l'antibiothérapie inefficace est définie par la persistance du germe malgré l'antibiothérapie.

Rôle de l'antibiothérapie inadéquate : un traitement initial inactif sur les germes responsables de la pneumonie survient fréquemment car la pneumonie est une maladie fréquemment associée à des germes multirésistants. Les traitements sont inadéquats initialement dans 25 à 45% des cas [32, 54-59].

Il existe parfois une confusion entre les deux rendant bien difficile l'interprétation de certaines études [57, 60].

Le rôle de l'adéquation de l'antibiothérapie est variable en fonction des études (Tableau 6).

Tableau 6 : Estimation de l'odds ratio (OR) de la mortalité intra-unité de soins intensifs (ICU) ou intra-hospitalière (hôpital) selon le type d'antibiothérapie instituée pour la pneumopathie nosocomiale

Référence	Adéquate	Inadéquate	OR (IC95%)	p
Dupont 2001[54]	21/55 (38%)	27/56 (48%)	1.5 (0.7-3.2) (ICU)	0.38
	26/55 (47%)	34/56 (61%)	1.7 (0.8-3.6) (hôpital)	0.21
Iregui 2002[56]	21/74 (28.4%)	23/33 (69.7%)	5 .8 (2.17-5.83) (hôpital)	<0.01
			Ajusté : 7.68 (4.50-13.09)	<0.001

De plus, même lorsque l'adéquation est basée sur une définition précise, les résultats des études récentes sont discordants. Il faut noter que dans l'étude de Iregui et al, [56] l'adéquation était mesurée sur l'ensemble des germes isolés de l'aspiration trachéale alors que dans l'étude de Dupont et al[54], l'adéquation était mesurée sur les germes retrouvés en quantité significative dans les prélèvements distaux. Pour expliquer ces discordances, il faut noter que (1) le nombre de germes différents retrouvés grâce à la première technique est beaucoup plus important que le nombre de germes retrouvés par la seconde [61], (2) la population d'étude était différente (mortalité du groupe correctement traité 28% vs. 47%), enfin (3) aucun ajustement n'était réalisé sur la sévérité de la pneumonie.

Rôle de l'antibiothérapie inadaptée

La non guérison des symptômes est associée avec un sur-risque de décès de façon constante.

Celle-ci est définie par la persistance de signes de sepsis sévère et du choc ou des défaillances d'organes. Cependant, il est difficile de connaître la part respective de la

pneumonie nosocomiale, de la maladie sous-jacente, de l'apparition d'une éventuelle autre affection nosocomiale dans la pérennisation des symptômes.

Rôle de l'antibiothérapie inefficace

Dans la majorité des cas, la mise en route d'une antibiothérapie adéquate entraîne une stérilisation rapide des voies aériennes inférieures [62, 63]. La persistance de germes est plus fréquente avec *P. aeruginosa* et avec le SDMR [62]. Il ne semble pas que la persistance du germe responsable de la pneumonie soit associée à un moins bon pronostic.

II-2-3 La méthode statistique utilisée est variable d'une étude à l'autre

Exposés-non exposés ou cohorte

Les études exposés-non exposés, appariées ou non, ne permettent de contrôler qu'un nombre limité de facteurs, dépendant du nombre de cas et de l'importance du nombre de patients non exposés potentiels. Certains facteurs pronostiques peuvent ne pas être contrôlés entre les exposés et les non exposés et/ou des patients non exposés peuvent ne pas être trouvés dans la population non–exposée potentielle.

Un exemple de la variabilité de la mesure du sur-risque de décès ou de la mortalité attribuable a été publié dans la littérature.

Le sur-risque de décès et la mortalité attribuable des hémorragies digestives cliniquement importantes ont été évaluées en réanimation sur 1666 malades (59 hémorragies digestives, 3.5% IC 95% : 2.7-4.6%) selon 4 méthodes : [64]

1- Taux brut de mortalité

2- exposés-non exposés : 1:1 apparié sur durée d'exposition, les dysfonctions d'organes 3 jours avant le saignement, la sévérité à l'admission (APACHE II), le diagnostic à l'admission et la durée de ventilation mécanique. L'estimation du sur-risque de décès était basée sur la méthode de Mantel-Haenszel où chaque strate était une paire.

3- Sur la cohorte de malade, les facteurs de risque de décès ont été estimés grâce à un modèle de Cox. Les patients étaient censurés à 28 jours. Les patients sortis dans un autre service de court séjour étaient considérés vivants sans événements, les patients sortis vers une autre réanimation étaient censurés le jour de leur sortie. Au risque α=0.10, une sélection des variables pronostiques a été réalisée en pas à pas. Les coefficients de la régression au dernier pas ont été utilisés pour créer un score utilisé pour apparier les patients ayant saigné et les autres. L'estimation des risques a utilisé les mêmes méthodes que (2).

4- Analyse utilisant un modèle de Cox en introduisant l'hémorragie digestive comme une covariable dépendante du temps sans autres covariables.

5- De la même manière que précédemment, les variables pronostiques ont été sélectionnées. Le nombre de dysfonctions d'organes au temps t à été introduit dans le modèle comme une covariable dépendante du temps. Enfin, l'hémorragie digestive a été introduite dans le modèle final comme une dernière covariable dépendante du temps.

Ces 4 types d'estimation aboutissent à des résultats de Risque relatif allant de 1.0 à 4.0 (tableau 7).

Tableau 7 : Estimation du risque relatif (RR) et du risque attribuable de décès selon le type d'analyse réalisée (d'après 64)

DC en réanimation	Estimation du RR (IC 95%)	Risque attribuable (IC95%)
Taux brut de mortalité (1)	2.2 (1.6-2.9) (20.9% vs 45.8%)	24 % (11.3-36.6%)
Exposés-non exposés apparié (2)	2.9 (1.6-5.5)	30.3% (15.2-45.3%)
Exposés-non exposés apparié (3)	1.8 (1.1-2.9)	20.3% (4.3-36.4%)
Modèle de Cox analyse univariée (4) Modèle de Cox : analyse ajustée (5)	4 .1 (2.6-6.5) 1.0 (0.6-1.7)	- -

Voir le texte ci avant pour le détail des modèles utilisés

La méthode brute (1) ignore totalement les facteurs confondants pouvant entraîner une estimation biaisée. L'étude exposés-non exposés (2) risque de ne pas tenir compte de facteurs de confusion importants qui n'ont pas servi de critères d'appariement et (3) peut sélectionner des variables liées et entraîner ainsi un sur-appariement.

Les analyses multivariées (3,5) peuvent ne mettre en évidence qu'une partie des facteurs pronostiques confondants, et l'oubli de certaines variables fondamentales peut altérer l'estimation du risque. Les phénomènes de sur-ajustement sont possibles. Enfin, dans le cas des modèles pour données censurées, l'estimation peut être biaisée si la force de mortalité de l'événement n'est pas constante au cours du temps.

Etude de cohorte : Choix du modèle

Les modèles de régression logistique et le modèle de Cox sont les deux modèles les plus fréquemment employés. Ils sont tout les deux sous-tendus par une relation log-linéaire entre le risque d'événement et les covariables explicatives.

Risque relatif et Odds ratio

Le modèle logistique mesure le rapport des côtes (ou odds ratio, OR) après une durée fixe d'exposition.

Pour le décès : $OR = \frac{P(D|E)/P(\bar{D}|E)}{P(D|\bar{E})/P(\bar{D}|\bar{E})}$

Alors que le risque relatif $RR = \frac{P(D|E)}{P(D|\bar{E})}$.

l'odds ratio ne peut donc s'interpréter comme un risque relatif que si le décès est rare.

Prenons par exemple la pneumonie nosocomiale :

Son incidence est de l'ordre de 20%. Imaginons que la mortalité des patients avec une pneumonie soit de 50% et que la mortalité du groupe sans pneumonie soit de 25% (tableau 8).

La mortalité est loin d'être négligeable mais correspond à une estimation plausible en réanimation. Dans ces conditions, l'OR est égal à 3 alors que le risque relatif est à 2. Ces divergences peuvent expliquer des différences dans l'estimation obtenue et dans les éventuels facteurs de risque (ou d'ajustement) sélectionnés (si ceux-ci sont retenus en fonction de la valeur du risque).

Tableau 8 : Comparaison de l'estimation de l'odds ratio (OR) et du risque relatif (RR) de mortalité des pneumonies, lorsque l'incidence de la pneumonie est de 20% et la mortalité des exposés et non exposés est respectivement de 50% et 25% (RR=2)

	Décédés	Vivants	Total
Pneumonie	10	10	20
Pas de pneumonie	20	60	80
	30	70	100

OR=(10/10)/(20/60)=3

RR=(10/(10+10))/(20/(20+60)=2

Ce calcul peut être généralisé à différentes valeur de l'odds ratio et différentes valeurs de la prévalence.

$OR=RR(\frac{1-R_0}{1-R_0RR})$ ou R_0 est le risque de décès chez les malades indemnes de pneumonie.

Tableau 9: Valeur de l'odds ratio en fonction du risque relatif et de la Proportion de décès chez les patients indemnes de pneumonie

R_0	*Valeur du risque relatif*				
	2	*3*	*4*	*5*	*8*
	Valeur de l'odds ratio				
1%	2.02	3.06	4.13	5.21	8.61
5%	2.11	3.35	4.75	6.33	12.67
10%	2.25	3.86	6.00	9.00	36.00
15%	2.43	4.64	8.50	17.00	+∝
20%	2.67	6.00	16.00	+∝	+∝
25%	3.00	9.00	+∝	+∝	+∝

Hazard ratio versus Risk ratio

- Le modèle de Cox mesure des rapports de risques 'instantanés' sur un intervalle petit en faisant l'hypothèse que ce rapport est constant au cours du temps.
- On a :

$$RR \approx HR = \frac{\lambda\left(t|Z=E\right)}{\lambda\left(t|Z=\bar{E}\right)} = \frac{\exp\left[\beta_x\left(Z=E\right)\right]}{\exp\left[\beta_x\left(Z=\bar{E}\right)\right]} = \exp\left(\beta_x\right)$$

si l'exposition (Z) est codée 1 et que la non exposition est codée 0.

L'estimation de HR est finalement la moyenne des HR (t).

Enfin, à noter une fois encore que l'interprétation du hazard ratio comme risque relatif suppose la fonction de risque constante au cours du temps et le risque absolu faible

Distribution du délai d'événement versus distribution de la prévalence de l'événement

Le modèle logistique ne prend pas en compte le temps de suivi des individus, ne modélisant que la probabilité d'événement. A l'opposé, le modèle de Cox modélise le risque instantané d'événement au cours du temps, prenant en compte les durées de suivi variables d'un individu à l'autre. Les malades qui n'ont pas développé l'événement en fin de suivi sont considérés comme exclus-vivants à cette date (définissant une censure à droite). Le modèle de Cox fait cependant l'hypothèse que cette censure est non informative, c'est à dire que la censure est indépendante du risque instantané d'acquérir un événement.

Pour l'exemple qui nous intéresse, la censure la plus courante est la sortie de réanimation. On fait l'hypothèse que le risque instantané de survenue du décès pour les individus sortis vivants de réanimation n'est pas modifié par la sortie, donc qu'il est le même que celui d'un individu resté en réanimation.

Les modèles sont t ils équivalents ?

Les facteurs de risques identifiés par les deux modèles seront probablement similaires si l'événement est rare ($OR \approx RR$), si l'effet des facteurs de risque est faible et la durée de suivie est courte.

Les durées de suivi en réanimation sont cependant très variables d'un patient à l'autre. Il semble donc préférable d'utiliser un modèle pour données censurées. Cependant, il est loin d'être évident que la censure en réanimation soit non informative. La mortalité post-réanimation a été évaluée par de nombreuses études et est très variable allant de 0 à plus de 30% en fonction notamment des pays et des ressources en soins intensifs.[65].

Il est donc pour l'instant difficile de choisir le « bon » modèle. Chacun est une simplification de la réalité et présente des imperfections. Les méthodes disponibles pour vérifier les hypothèses sous-jacentes aux modèles sont peu puissantes. Il est

probable que l'on puisse disposer d'estimation fiable si plusieurs types d'approches donnent des résultats similaires (donc robustes).

II-2-4 Le principal facteur de confusion, l'évolution du malade en cours de séjour

La gravité des patients, liée à la mortalité, est considérée comme un des principaux facteurs de risque d'infection nosocomiale.

La gravité mesurée par les scores de gravité généraux utilisés en réanimation est un facteur de risque de pneumonie nosocomiale et un facteur de risque de décès, si bien que la gravité des patients de réanimation joue le rôle de facteur de confusion dans l'appréciation de la relation entre la pneumonie et le décès. De fait, de nombreuses études exposés-non exposés ont utilisé un appariement ou un ajustement sur des scores de gravité généraux mesurés à l'admission comme le SAPS II ou l'APACHE [13, 16, 17, 20, 23].

La prise en compte de la gravité initiale est logique. Cependant, l'utilisation de scores de gravité généraux comme témoin de la gravité des malades induit probablement un biais.

En effet, ces scores ont été construits sur de grandes populations de malades dont la durée de séjour en réanimation était dans plus de la moitié des cas inférieure à 3 jours. Comme, par définition, la pneumonie nosocomiale ne peut pas survenir avant la 72ème heure d'hospitalisation, la population exposée au risque d'infection nosocomiale n'est pas le reflet de la population générale de réanimation. Il est de plus démontré [66] que les propriétés des scores, en particulier leur discrimination, sont rapidement altérées si la durée de séjour s'allonge. Ainsi, au 14ème jour, le score de gravité à l'admission n'est plus un prédicteur de mortalité hospitalière [66] (tableau 10).

Tableau 10 : Utilisation des ressources et performance des modèles de survie en fonction de la durée de séjour en réanimation (adapté de [66])

IGS II et séjours prolongés

	<1 jour	<4 jours	>7 jours	>14 jours	>30 jours
% patients	41%	81%	10%	4%	1%
% journées	8%	34%	52%	33%	13%
SAPS II vivants	21	22	38	35	32
SAPS II décédés	55*	50*	43*	38	33
AUC-ROC	0.91	0.87	0.62	0.59	0.54

(*): $p<0.05$

Base de données finlandaise, 23953 Patients,
40.6% Post-op.
Durée de séjour médiane: 1.3 jours

De plus, les scores de gravité sont mal corrélés à la durée de séjour en réanimation [67, 68] et donc au temps d'exposition au risque de pneumonie nosocomiale. La durée d'exposition au risque et en particulier la durée de ventilation est pourtant le principal facteur de risque de pneumonie nosocomiale.

Pendant la première semaine d'hospitalisation en réanimation, la gravité le dernier jour où elle est disponible est le prédicteur de la survie le plus important. Sur la base APACHE III, [69] le score de gravité physiologique le jour même contribuait pour 54% dans la prédiction de mortalité, alors que le score mesuré à l'admission n'expliquait que 5% du modèle.

Il devient donc probable qu'un ajustement utilisant la gravité à l'admission, même s'il est associé à un ajustement sur la durée d'exposition au risque, est insuffisant. A l'extrême, les scores de gravité initiaux ne sont plus capables de distinguer parmi les patients avec une pneumonie nosocomiale à *P. aeruginosa* ceux qui vont survivre de ceux qui vont décéder [16].

De plus, l'ajustement sur les scores initiaux ne tient pas compte de l'évolution des patients entre leur arrivée en réanimation et le moment où ils sont suspects de pneumonie.

On conçoit qu'il faille tenir compte de l'évolution de la gravité des patients entre l'admission et le jour, parfois très éloigné, où ils vont être atteints d'une pneumonie.

A l'heure actuelle, très peu d'études ont tenté d'évaluer l'évolution de la gravité dans les premiers jours de réanimation comme facteur de risque d'acquisition d'une infection nosocomiale et tenté de tenir compte de l'évolution de la gravité dans l'estimation de la mesure de la surmortalité associée aux infections nosocomiales.

Dans une étude récente, Girou et coll [17]ont cependant confirmé que les patients qui allaient présenter une pneumonie nosocomiale s'aggravaient alors que ceux qui n'allaient pas en présenter amélioraient leurs dysfonctions d'organes en cours de séjour en réanimation. Dans cette étude le seul facteur de risque dynamique de pneumonie nosocomiale était la persistance d'une défaillance neurologique à J3 (figure 2).

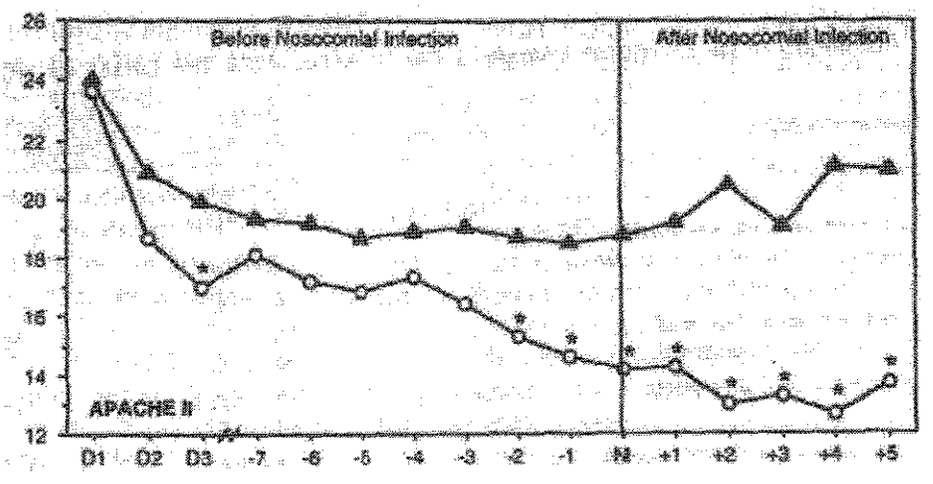


Figure 2 : Evolution du score de gravité APACHE II de malades admis en réanimation selon qu'ils ont ou non développé une infection nosocomiale (d'après 16)

Cependant, aucune étude ne permet de démontrer que des scores de gravité ou de dysfonction d'organes, validés le plus souvent le jour de l'admission, sont utilisables comme paramètre d'ajustement reflétant la gravité en cours de séjour. Il est d'ailleurs important de mentionner qu'aucun score de dysfonction d'organes ou de gravité, mesurable de façon quotidienne, n'a

été complètement validé. Certains travaux préliminaires ont étudié la valeur respective des différentes dysfonctions d'organes dans le pronostic des patients [69-72].

Les patients développent de nombreux événements indésirables et infections nosocomiales qui peuvent être liés à la mortalité

Nous avons étudié [35] les conséquences de la pneumonie nosocomiale sur une cohorte de 387 patients consécutifs (168 décès) ventilés plus de 48 heures. Les patients ont été suivis de leur admission à la sortie de la réanimation. En cas de suspicion clinique de pneumonie nosocomiale, les patients bénéficiaient d'une fibroscopie avec brosse de Wimberley et lavage alvéolaire. En fonction des résultats de ces examens, les patients recevaient un traitement antibiotique adapté ou non. Parmi les 387 patients, 112 (28.9%) ont présenté une suspicion clinique de pneumonie (SusPN) et la pneumonie a été confirmée chez 56 d'entre eux (C-PN).

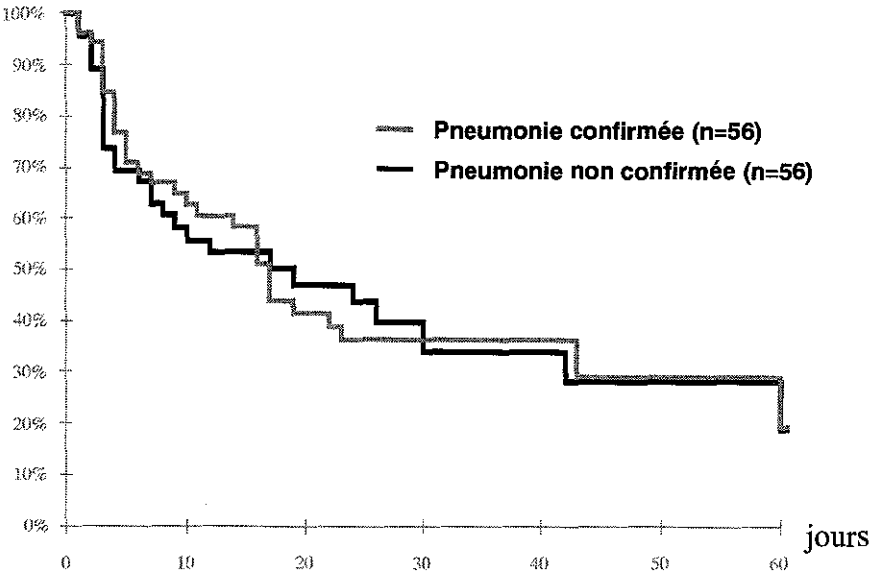
Un modèle de Cox a été construit en ajustant sur les covariables pronostiques présentes dans les 48 premières heures d'hospitalisation et en introduisant séparément puis simultanément la pneumonie clinique et la pneumonie clinique confirmée par les prélèvements comme 2 covariables dépendantes du temps. Dans cette analyse, seul le premier épisode de pneumonie a été pris en compte. Après ajustement sur le score de Mc Cabe, l'APACHE II, le choc dans les 48 premières heures, l'utilisation de sédatif, et l'absence de nutrition entérale dans les premières 48 heures, SusPN (HR= 2.1 p=0.0001) et C-PN (HR=1.8, p=0.007) étaient associées à un risque plus élevé de décès. Cependant, si les deux covariables étaient introduites simultanément dans le modèle, seule la suspicion clinique de pneumonie était associée au pronostic, la confirmation n'apportant pas de valeur pronostique supplémentaire. Enfin, avec ou sans ajustement sur les paramètres pronostiques au moment de la suspicion de pneumonie, la mortalité des patients avec une SusPN non confirmée et avec une C-PN était identique (figure 3 ; HR=1.0 , P=0.96).

Ce résultat troublant peut être lié à plusieurs facteurs :

1- Les patients suspects de pneumonie nosocomiale (pneumonie clinique) ont tous une pneumonie, que les prélèvements bactériologiques soient positifs au seuil retenu ou non. Les prélèvements quantitatifs distaux seraient alors peu sensibles. Une littérature considérable et très contradictoire sur le diagnostic des pneumonies nosocomiales ne permet pas d'éliminer formellement cette hypothèse [9]. Cependant, de nombreuses études post mortem ont confirmé l'absence de pneumonie histologique chez des patients ayant une pneumonie clinique [73-75], la moitié des patients ayant des pneumonies cliniques non confirmées bactériologiquement ont guéri en l'absence de traitement antibiotique.

2- La pneumonie nosocomiale prouvée bactériologiquement n'entraîne pas de sur-risque de décès. En fait c'est le terrain sous-jacent, l'évolution des patients en réanimation qui sont responsables du décès. Les patients mourraient non pas d'une pneumonie nosocomiale mais avec une pneumonie nosocomiale. Cette hypothèse est difficile à accepter complètement car on sait créer une pneumonie nosocomiale mortelle chez l'animal, et la prévention de la pneumonie nosocomiale peut limiter la mortalité des patients, au moins dans certains cas [76].

3- Enfin, les patients ayant une pneumonie nosocomiale clinique non confirmée bactériologiquement peuvent avoir d'autres pathologies grevant tout autant le pronostic et responsable de fièvre, d'un état septique sévère et d'un infiltrat radiologique nouveau.



Dèces chez les patients avec une pneumonie clinique confirmée bactériologiquement ou non (Daprès 35)

Figure 3 : estimation de la survie des malades avec pneumonie suspectée, qu'elle soit secondairement confirmée ou non

Il existe en effet de nombreux arguments pour penser que d'autres événements indésirables peuvent jouer un rôle de facteurs confondants plus ou moins évidents.

Ainsi, l'extubation accidentelle des patients entraîne un risque de décès immédiat par difficulté de réintubation et un risque d'inhalation massive de micro-organismes lors de la réintubation en urgence, et donc en conséquence de pneumonie nosocomiale. L'hémorragie digestive par ulcère de stress entraîne la mise en route d'un traitement anti-acide entraînant une élévation du pH de l'estomac favorisant la pullulation microbienne gastrique. A la faveur de micro-inhalation et d'un reflux toujours présent, le traitement anti-H2 est ainsi un facteur de risque reconnu de pneumonie nosocomiale [9, 42].

En conclusion, La mortalité attribuable des infections nosocomiales, de nombreuses questions...

L'évaluation du sur-risque de décès associé à l'infection nosocomiale ou plus généralement à l'événement indésirable en réanimation est bien difficile.

Concernant l'infection nosocomiale,

1- Les définitions utilisées sont variables selon les études, les pays ou les régions.

2- L'incidence estimée est variable en fonction des populations explorées (facteurs de risque particulier, case-mix, gravité (facteurs endogènes))

3- L'impact sur la mortalité est variable en fonction de la virulence des germes en cause, la précocité et l'adéquation du traitement antibiotique

4- La liaison entre infection nosocomiale et mortalité est difficile à établir car de nombreux événements intercurrents sont des événements pronostiques ou même sont des facteurs de risque d'infection ...

5- Les modèles utilisés sont imparfaits et assortis d'hypothèses sous-jacentes fortes parfois difficilement vérifiables.

Une infection surajoutée est à l'évidence responsable d'une certaine morbi-mortalité.

Cependant, il est probable que l'estimation de la sur-mortalité associée à l'infection nosocomiale (à condition qu'elle soit correctement et précocement traitée) ait été sur-évaluée dans la littérature car les études publiées n'ont pas pris en compte le fait que les patients qui développent une infection nosocomiale sont les patients qui évoluent mal et qui sont le plus à risque d'autres événements intercurrents [77].

III- Développements réalisés dans le cadre de la thèse

III-1 Développement et validation des modèles pronostiques utilisables chez les malades exposés aux infections nosocomiales

La population des patients exposés au risque d'infection nosocomiale n'est pas celle qui a été utilisée pour valider les scores pronostiques utilisés en réanimation.

Cette première réflexion a abouti à la conception et à la création d'un score de gravité chez les patients hospitalisés en réanimation plus de 3 jours calendrier, qui sont les seuls qui, par définition, sont à risque d'infection nosocomiale. Ce travail a été réalisé sur la base multicentrique OUTCOMEREA et validée sur un échantillon externe de malades inclus dans 24 réanimations françaises (**cf. annexe1** : Timsit JF, Fosse JP, Troché G, De lassence A, Alberti C, Garrouste-Orgeas M, Azoulay E, Chevret S, Moine P, Cohen Y - Accuracy of a composite score using daily SAPSII and LOD scores for predicting hospital mortality in ICU patients hospitalized for more than 72 hours- Intens Care med 2001; 27:1012-1021).

Une population de 893 malades hospitalisés plus de 72 heures dans 4 services a été utilisée pour construire le modèle. Il s'agissait d'une population d'âge médian de 66 ans. Six cent vingt-huit (70%) patients étaient hospitalisés pour un motif médical. Quatre-cent vingt (47%) patients provenaient d'une autre unité de cours séjour. Le taux de mortalité en réanimation était de 22.7 % et le taux de mortalité à l'hôpital de 30%. Les dysfonctions d'organes ont été définies grâce au score de gravité SAPSII et au score de dysfonction d'organe LOD, mesurés les 3 premiers jours d'hospitalisation .

Les paramètres pronostiques ont été inclus dans un modèle de régression logistique. La gravité le premier, le deuxième et le troisième jour, les maladies chroniques, l 'état antérieur, la notion de transfert d'une autre unité étaient les paramètres pronostiques les plus importants.

Dans un but de simplification et d'utilisation du modèle final, les scores tels qu'ils onté été publiés plutôt que leurs composantes ont été utilisés. De plus, pour éviter des phénomènes de multicolinéarité[78], plutôt que les scores eux-mêmes, ce sont les variations de scores entres J1 et J2 et entre J2 et J3 qui ont été introduites dans le modèle. Enfin, dans un premier modèle, les maladies chroniques ont été introduites séparément, dans un deuxième modèle, nous n'avons introduit qu'une variable binaire indiquant la présence d'au moins une maladie chronique. Le choix entre les deux modèles non emboîtés a été effectué sur le critère d'Akaike [79].

La calibration du modèle a été mesurée grâce à la méthode de Hosmer-Lemeshow[80]. La discrimination du modèle a été évaluée par l'utilisation de courbes ROC [81].

Nous avons comparé les propriétés du modèle créé à celles des scores LOD et SAPS II mesurés à l'admission.

La validation du modèle s'est effectuée en 2 phases : un rééchantillonnage de la base initiale par la technique du bootstrap (500 échantillons indépendants) et une validation sur une base de 392 malades consécutifs hospitalisés dans 24 autres centres de réanimation en France. L'analyse a été effectuée grâce aux logiciels S.A.S. 6.12 (SAS institute, Cary, NC) et au logiciel MedCalc 5.00 (Medcalc, Ghent, Belgium) .

Le modèle créé (tableau 11) a été comparé aux modèles pronostiques classiques (SAPS II et MPM 72). Sa discrimination était meilleure que celles des scores mesurés à l'admission. Sa calibration, même dans l'échantillon de validation externe, était satisfaisante (tableau 12).

Tableau 11 : Modèle pronostique pour la mortalité hospitalière développé à partir d'une régression logistique (échantillon de construction, n= 893, 268 décès hospitaliers)

	Parametres	Odds ratio IC 95%	P (Wald)	Odds ratio IC 95% (Bootstrap)
Intercept	-4.44		0.0001	
Transfer from ward (0/1)	0.5543	1.74 [1.25-2.42]	0.001	[1.253-2.453]
LOD à l' admission	0.1536	1.16 [1.085-1.253]	<0.0001	[1.093-1.276]

SAPS II à l'admission	0.0388	1.04 [1.027-1.053]	<0.0001	[1.026-1.053]
Maladie chronique (0/1)	0.8507	2.34 [1.677-3.269]	<0.0001	[1.622-3.296]
Augmentation du SAPS entre J3 et J3	0.4161	1.516 [1.04-2.22]	0.032	[1.055-2.373]
Augmentation du LOD entre J3 et J3	0.6940	2.00 [1.29-3.11]	0.0002	[1.292-3.019]

Tableau 12 : comparaison des performances des différents modèles (scores TRIO, SAPS II et MPM 72) de prédiction de la mortalité hospitalière

	AUC-ROC (95 % CI)	Hosmer-Lemeshow C statistic (p value)
Echantillon de construction		
SAPS II	0.744 (0.714-0.773)	37.4 (0.001)
LOD at admission	0.681 (0.646-0.714)	21.2 (0.01)
MPM72	0.786 (0.757-0.812)	22.3 (0.01)
Score TRIO	0.794 (0.766-0.820)	5.56 (0.70)
Echantillon de validation		
SAPS II	0.741 (0.688-0.789)	19.8 (0.02)
LOD at admission	0.725 (0.668-0.777)	32.2 (0.002)
MPM72	0.814 (0.774-0.854)	18.2 (0.03)
Score TRIO	0.826 (0.780-0.867)	7.14 (0.5)

Nous proposons d'utiliser cet outil pour mesurer la gravité lors des tentatives d'estimation de la mortalité attribuable à un événement survenant après la 72èmeheure.

Commentaires sur le choix des variables : L'utilisation du score de dysfonction d'organes LOD et du score de sévérité SAPS II simultanément dans un modèle composite doit être discutée. En effet, ces deux modèles ont été conçus sur la même base de données, les items qui les composent ne sont, que pour une partie, différents. A priori, ces deux scores sont colinéaires. Nous aurions pu décider de ne pas les introduire simultanément dans le modèle. Nous avons fait le choix opposé car (1) les seuils utilisés pour les variables les composant ne sont pas identiques, (2) la proportion de la variance du SAPS II expliquée par le score LOD n'était que de 60%, et (3) lorsque les 2 variables étaient simultanément introduites dans le même modèle, les 2 covariables étaient sélectionnées, le modèle convergeait et la déviation

standard des estimateurs était petite. Il est probable que ce résultat retrouvé sur la base SAPS II et sur la base European Sepsis (données non publiées) soient expliquées par les interactions entre les variables constituant les scores qui ne sont pas prises en compte.

III-2 Validation de l'utilisation des scores de dysfonction d'organes LOD et SOFA mesurés quotidiennement en cours de séjour en réanimation : (**cf. annexe 2** Timsit JF, Fosse JPh, Troche G, De lassence A, Alberti C, Garrouste Orgeas M, Bornstain C, Adrie C, Cheval C, Chevret S for the Outcomerea study group – Calibration and discrimination by daily LOD scoring comparatively to daily SOFA scoring for predicting hospital mortality in critically ill patients – Crit Care Medicine 2002; 30:2003-2013)

Afin de palier à l'absence de tout type de données concernant les scores mesurant les dysfonctions d'organes dans leur utilisation quotidienne, une validation du score de SOFA et du score LOD mesuré entre le premier et le septième jour calendaire a été réalisée.

La base de données comportait 1685 malades (511 décès hospitaliers, SAPS II médian à l'entrée : 38) pour lesquels les différents éléments des scores étaient saisis de façon quotidienne par des médecins seniors dans 6 services de réanimation français.

La performance de ces scores a été mesurée au jour J en tenant compte des malades encore hospitalisés à J+1. La discrimination des 2 scores de J1 à J7 était satisfaisante (aire sous la courbe ROC entre 0.729 et 0.784). Il n'y avait pas de différence de discrimination entre les 2 scores. La cohérence interne des points attribués pour chaque dysfonction d'organes, chaque jour et pour chacun des 2 scores était correcte. De même, la mortalité observée augmentait avec le nombre de dysfonctions d'organes retrouvé. La calibration des modèles originaux était mauvaise et nécessitait une recalibration en introduisant le score global dans un modèle de

régression logistique. Dans ces conditions et quel que soit le jour, les 2 scores étaient correctement calibrés.

Cependant, la part respective des différentes dysfonctions d'organes dans les 2 scores n'était pas identique. Le poids de la défaillance hématologique était plus important dans le score LOD et augmentait au fur et à mesure des jours. Le poids de la défaillance neurologique était plus important avec le score SOFA. Pour cette raison, l'introduction des points respectifs obtenus pour chaque dysfonction d'organes permettait d'obtenir une meilleure discrimination des deux scores et une bonne calibration.

Cette étude montre que la discrimination de ces scores mesurés de façon quotidienne reste correcte et similaire à celle de la mesure initiale.

Nous considérons que les scores de gravité initiaux (même mesurés au troisième jour) sont des marqueurs insuffisamment discriminants de la mortalité des patients hospitalisés beaucoup plus longtemps. Ces résultats autorisent d'utiliser le score LOD ou le score SOFA à un jour donné (au moins dans la première semaine) comme facteur d'ajustement ou d'appariement dans les études de cohorte ou exposés-non exposés réalisées pour estimer le sur-risque de mortalité associé à des événements survenant tard au cours de l'hospitalisation.

III-3 Utilisation des scores évolutifs comme facteur d'ajustement

III-3-1 : Etude de cohorte exposé-Non exposés appariée avec analyse par régression logistique conditionnelle: Impact des pneumonies nosocomiales à germes réputés peu pathogènes sur le pronostic des patients de réanimation. (**cf annexe 3**: Lambotte O, Timsit JF, Garrouste-Orgeas M, Misset B, Benali A, Carlet J – Distal bronchial samples with commensals in suspected ventilator-associated pneumonia – Chest 2002 ; 1387-1397)

Nous avons réalisé une étude de cohorte pour évaluer les conséquences en termes de mortalité des pneumonies à germes réputés peu pathogènes.

Sur un collectif de 1955 patients consécutifs hospitalisés, pendant une période de 10 ans, en réanimation à l'hôpital St Joseph et ventilés, 369 (18.9%) ont présenté une pneumonie nosocomiale. Pour 33 (32 patients) de ces épisodes, les seuls germes retrouvés étaient réputés peu pathogènes (Staphylocoques coagulase négatif, streptocoques non hémolytiques, *Neisseria* spp, *Haemophilus* (non *influenzae*)). Pour 28 des 32 patients, l'ensemble des données des dossiers était disponible et il n'existait pas d'immunodépression. Dans 22 cas, un traitement antibiotique dirigé contre ces bactéries a été mis en route.

Pour évaluer les conséquences de cet événement :

Les dossiers ont été revus par 3 médecins experts, de façon indépendante.

L'évolution des scores de dysfonction d'organes au moment de l'événement a été reconstituée

Une étude exposé- non exposé a été réalisée :

Pour un taux brut de mortalité de 35% des patients, 2 témoins par cas étaient nécessaires pour mettre en évidence une augmentation du risque de décès d'un facteur 2 avec une puissance de 0.80 et un risque d'erreur de type I de 0.05.

Chaque patient porteur d'une pneumonie a donc été apparié avec 2 patients n'ayant pas fait de pneumonie nosocomiale, de même mortalité prédite (±10%), de même sexe, hospitalisé pendant la même période, ventilé mécaniquement au moins aussi longtemps que les patients porteurs d'une pneumonie au moment où celle-ci a été acquise.

La sélection des témoins a été réalisée à partir du fichier du service à l'aide d'une macro-commande écrite sous SAS. Les témoins indemnes de pneumonie nosocomiale étaient sélectionnés automatiquement en partant du cas ayant la durée d'exposition au risque la plus courte.

Pour chaque patient porteur d'une pneumonie et leurs témoins respectifs, le score de dysfonction d'organe LOD a été relevé à l'admission, le jour de la pneumonie (pour les témoins, le jour correspondant à la même durée de ventilation mécanique) 3 jours et 7 jours avant la pneumonie.

Les 3 experts ont retenu à l'unanimité le diagnostic de pneumonie nosocomiale dans 23 cas.

Le score LOD s'aggravait significativement au moment de la pneumonie chez les cas alors qu'il restait inchangé chez les témoins appariés.

Dix des 28 cas sont morts (36%), dans 2 cas avec une pneumonie à l'histologie.

Une régression logistique conditionnelle a été effectuée en utilisant la procédure GENMOD de SAS 6.12. Dans ces conditions, la pneumonie nosocomiale n'entraînait pas de sur-risque de décès (OR : 1.19 (IC 95% : 0.41-3.46)) mais était associée à une augmentation significative de la gravité (telle que mesurée par les scores de dysfonction d'organe) et à une prolongation du séjour en réanimation moyenne de 6 jours.

III-3-2 : Etude de cohorte exposé-non exposés appariée avec analyse par modèle de Cox marginal: Mortalité induite par les bactériémies sur cathéters avec prise en compte de la gravité en cours de séjour avant l'événement (**cf. annexe 4** : Soufir L, Timsit JF, Mahe C, Carlet J, Regnier B, Chevret S - Attributable mortality and morbidity of catheter related bacteremia in critically ill patients - A matched risk adjusted cohort study. Infect Control Hosp Epidemiol 1999;20:396-401)

L'infection bactériémique liée au cathéter semble être un bon candidat comme marqueur de qualité des soins dans les services de réanimation. En effet, (1) sa définition est relativement consensuelle, (2) les facteurs de risque sont essentiellement liés au cathéter et

peu au terrain et à la gravité sous jacente. Afin d'être un bon indicateur qualité, il restait à savoir si on pouvait imputer à l'infection bactériémique liée aux cathéters un risque de décès.

Nous avons réalisé une étude de cohorte exposé-non exposé cherchant à évaluer la surmortalité des septicémies sur cathéter veineux centraux en réanimation. Nous avons utilisé les bases de données de 2 services de réanimation suivant prospectivement les infections liées aux cathéters, cultivant l'ensemble des cathéters centraux et ayant les mêmes stratégies de diagnostic et de traitement. Sur 3587 patients, 42 ont présenté une infection de cathéter (11.7 pour 1000 admissions). Pour 38, les dossiers permettaient de reconstituer l'ensemble des scores de gravité à l'admission et en cours de séjour. Les sujets exposés et les non exposés étaient appariés sur la gravité à l'admission et la durée d'exposition au risque. Nous avons par ailleurs mesuré la gravité des exposés 3 et 7 jours avant la septicémie sur cathéter et nous l'avons comparée à la même mesure effectuée chez les non exposés. Nous avons pu utiliser un modèle de Cox marginal permettant la prise en compte de l'appariement [82].

Cette étude a montré que les scores de gravités étaient plus élevés chez les exposés que chez les non exposés 3 et même 7 jours avant la date de l'infection de cathéter. L' odds ratio de décès chez les exposés, ajusté sur la gravité à l'admission était estimé à 2.1 (IC à 95% : 1.08 – 3.73). Mais, après ajustement sur l'évolution des scores de gravité et leur valeur 3 et même 7 jours avant l'infection, le sur-risque de décès n'était plus que de 1.3 (IC à 95% : 0.69-2 .46).

Commentaires :

Le modèle de Cox marginal permet de tenir compte de l'appariement et utilise une estimation de la variance robuste prenant en compte la corrélation entre délais de survie d'une même paire. Il est d'ailleurs intéressant de noter que dans ce travail, l'appariement sur la gravité initiale n'améliore que très peu la ressemblance entre les paires. Cet appariement

pouvant même être considéré comme superflu. Il est pour l'instant classique mais pourrait être rediscuté.

Par ailleurs, l'ajustement sur la gravité 3 ou 7 jours avant l'infection nosocomiale est critiquable. En effet, il n'est pas certain que la gravité 3 jours avant l'infection ne soit pas due à la phase « d'incubation » de la maladie. Cependant, les scores 7 jours avant l'infection ne sont pas influencés par celle-ci.

III-3-3 : Etude de cohorte avec analyse par modèle de Cox tenant compte de l'évolution de la gravité les 4 premiers jours – Impact des pneumonies nosocomiales tardives sur la mortalité des patients de réanimation. – Prise en compte de l'effet centre et de l'effet de l'adéquation initiale de l'antibiothérapie (**cf. annexe 5 :** Moine P, Timsit JF, de Lassence A, Troche G, Fosse JP, Alberti C, Cohen Y, for the outcomerea study group – Mortality associated with late-onset pneumonia in ICU: Result of a multi-center cohort study – Intensive Care Med 2002;28:154-163)

Comme nous l'avons vu, la surmortalité induite par les pneumopathies nosocomiales en réanimation reste l'objet d'une importante controverse. La sévérité initiale des patients, l'évolution de cette gravité au cours du séjour, la durée de séjour en réanimation avant la survenue de la pneumopathie et les infections nosocomiales concomitantes sont autant de facteurs influençant la mortalité en réanimation. De plus, la morbi-mortalité induite par les pneumopathies nosocomiales est largement influencée par la population affectée (case-mix), la stratégie diagnostique, le délai avant le diagnostic, le délai avant la mise en route d'une antibiothérapie, le microorganisme causal et l'efficacité de l'antibiothérapie initiale. Les pneumopathies nosocomiales tardives (PNT) (survenant plus de 96 heures après l'admission en réanimation) pourraient ainsi induire une surmortalité liée à la plus grande fréquence de

micro-organismes multirésistants et un risque plus important d'antibiothérapie inadéquate inefficace. Le but de ce travail est l'étude des facteurs de risque de mortalité des patients en réanimation, notamment des pneumopathies nosocomiales tardives, en prenant en compte tout particulièrement la sévérité initiale et l'évolution de la sévérité au cours des quatre premiers jours post-admission et le caractère adéquat de l'antibiothérapie empirique initiale prescrite dans le cadre de ces pneumopathies nosocomiales tardives.

Il s'agit d'une étude prospective, opérationnellement, multicentrique, conduite dans 4 réanimations médicales et chirurgicales pendant 18 mois. Les patients âgés de plus de 16 ans et hospitalisés plus de 96 heures en réanimation sont inclus. Les éléments cliniques, biologiques, radiologiques et thérapeutiques, et la sévérité (SAPS II et LOD score) sont enregistrés quotidiennement de l'admission à la sortie de réanimation des patients. Le recueil est standardisé et effectué quotidiennement par les médecins seniors après mise au point concertée de l'ensemble des définitions. Une pneumonie nosocomiale tardive est suspectée devant l'apparition après plus de 96 heures post-admission en réanimation d'une nouvelle image radiographique pulmonaire persistante associée à au moins un des éléments cliniques ou biologiques suivants : Sécrétions trachéobronchiques purulentes ; hyperthermie > 38°5C ou hypothermie < 36°5C ; ou leucocytose > $10x10^9$/l ou < $4x10^9$/l. Une fibroscopie bronchique est alors réalisée avec un PDP dirigé ou un brossage protégé ou un lavage bronchoalvéolaire avant toute modification de l'antibiothérapie. Une pneumonie nosocomiale tardive est confirmée si les seuils de culture sont respectivement ≤ 10^3 cfu/ml, ≤ 10^3 cfu/ml et ≤ 10^4 cfu/ml.

Sept cent soixante quatre patients hospitalisés plus de 96 heures en réanimation sont étudiés. Le taux de mortalité globale est de 25 %. 89 patients (12 %) ont développé une pneumopathie nosocomiale tardive (69 patients (77.5 %) ont développé leur pneumopathie 7

jours ou plus après leur admission). Le taux de mortalité de cette population est 47 %. Le taux de mortalité standardisé (TMS) des patients présentant une pneumopathie nosocomiale tardive est 1,55 pour un TMS de 0,84 chez les patients ne développant pas de pneumopathie. Les facteurs de risque en analyse multivariée d'acquisition d'une pneumopathie nosocomiale tardive dans cette population sont l'existence d'une pneumonie à l'admission en réanimation (OR 2,79 ; IC 95% 1,42-3,65 : p = 0,0006) et un LOD score à 48 heures post-admission > 4 (OR 2,58 ; IC 95% 1,65-4,05 : p < 10-4). Les facteurs de risque de mortalité dans cette population de réanimation hospitalisée plus de 96 heures sont, en analyse multivariée, une score McCabe > 1, la sévérité des 24 premières heures post-admission mesurée par le SAPS II, l'aggravation de cette sévérité au cours des 4 premiers jours mesurée par une augmentation du SAPS II entre J1 et J2, J2 et J3, et J3 et J4. Après ajustement sur les paramètres pronostiques sélectionnés, la survenue d'une pneumonie nosocomiale tardive est significativement associée à un sur-risque de mortalité (HR = 1,53, IC 95% 1,02 - 2,3 ; p = 0,04) dans cette population. Néanmoins, lorsque le caractère adéquat, ou non adéquat, du traitement antibiotique empirique initial est introduit dans le modèle, le sur-risque de mortalité n'est observé que si le traitement antibiotique initial est inadéquat (HR = 1,69, IC 95% 1,08-2,65 ; p = 0,022) et non lorsque l'antibiothérapie initiale était adéquate (HR = 1,44, IC 95% 0,75-2,76 ; p = 0,27). Ces résultats justifient pleinement l'utilisation après prélèvements à visée bactériologiques d'une antibiothérapie à large spectre en première intention chez les patients hospitalisés en réanimation depuis 4 jours et suspects de développer une pneumopathie nosocomiale tardive.

III-3-4 Evaluation des conséquences de l'acquisition d'un portage ou d'une infection à staphylocoques aureus résistant à la meticilline (SARM) en réanimation (**cf. annexe 6** Garrouste-Orgeas M, Timsit JF, Kallel H, Benali A, Dumay MF, Paoli B, Misset B, Carlet J –

Colonization with methicillin resistant *Staphylococcus aureus* (MRSA) in ICU patients : impact upon morbidity , mortality and glycopeptide use – Infect Control Hosp epidemiol 2001; 22: 687-692)

D'autres indicateurs de qualité infectieux pourraient être utilisés en réanimation. L'acquisition de *Staphylocoques aureus* résistant à la meticilline (SARM) est directement liée à une transmission manuportée. La mesure de cette variable est simple et sa définition claire et consensuelle. L'acquisition de SARM est considérée comme un des paramètres de qualité des soins à surveiller en réanimation. Les conséquences du portage de SARM sur le pronostic sont cependant insuffisamment évaluées.

But de l'étude : Evaluation des conséquences du portage de SARM chez les patients de réanimation : Mortalité, risque d'acquisition d'infection à staphylocoques dorés, consommation de Glycopeptides.

Méthodes : Le portage nasal de SARM est réalisé chez tous les patients à l'admission et toutes les semaines dans l'unité de réanimation de l'hôpital saint Joseph. Par ailleurs, un suivi prospectif de l'ensemble des infections nosocomiales à staphylocoques méticilline sensible (SASM) et résistants (SARM) est effectué. Enfin, l'utilisation quotidienne de glycopeptides de chaque patient était surveillée par le comité du médicament.

Nous avons évalué, grâce à un modèle de Cox, le sur-risque de décès induit par le portage à l'admission ou l'acquisition de SARM. Cette variable était introduite dans le modèle comme une covariable dépendante du temps.

Afin d'apprécier la morbidité de l'acquisition d'un SARM, nous avons aussi effectué un autre modèle afin d'évaluer le risque de survenue d'une infection à staphylocoque doré.

Enfin, nous avons évalué quelle était la consommation de glycopeptides associée au portage de SARM sans infection, celle associée à une infection à SARM et celle des patients n'étant pas colonisés à SARM.

Cette étude ne retrouve pas de sur-risque de décès associé au portage de SARM. Par contre, le portage de SARM est associé à une plus forte incidence d'infection nosocomiale à *Staphylococcus aureus* et entraîne une augmentation significative des prescriptions empiriques et des prescriptions documentées de glycopeptides.

Commentaires : La mortalité est peut être un marqueur très peu sensible des conséquences des événements indésirables. Dans cette étude, il n'existe certes pas de conséquences directes du portage de SARM pour le patient mais ce portage augmente l'utilisation probabiliste de vancomycine.

L'utilisation accrue de vancomycine a été associée avec l'augmentation du risque d'acquisition de germes multirésistant (entérocoques résistant à la vancomycine (ERV) en particulier) et à un certain nombre d'effets secondaires.

III- 3- 5 Evaluation des conséquences des extubations iatrogènes sur l'acquisition des pneumopathies nosocomiales et le pronostic des patients de réanimation. Utilisation d'un modèle de Cox avec covariables dépendantes du temps. (**cf annexe 7 :** Delassence A, Alberti C, Azoulay E, Le Mierre E, Cheval C, Vincent F, Cohen Y, Garrouste Orgeas M, Adrie C, Troche G, Timsit JF for the Outcomerea study group – Impact of unplanned extubation and reintubation after weaning on nosocomial pneumonia risk in the intensive care unit – Anesthesiology 2002; 97 : 148-156)

Sur un collectif de 750 (7953 jours de ventilation mécanique) patients ventilés suivis prospectivement, les conséquences des extubations iatrogènes comme facteur de risque de pneumonie nosocomiale et comme facteur pronostique ont été étudiées. La durée médiane de ventilation était de 7 jours. La mortalité en réanimation était de 36.8% (276 décès) et à l'hôpital de 43.9% (329 décès).

Cent cinquante et un patients ont eu au moins un épisode d'extubation iatrogène (16.4 pour mille jours de ventilation mécanique) (51 auto-extubations chez 38 patients, 24 extubations accidentelles chez 22 patients, et 56 échecs d'extubation programmée chez 45 patients) . L'influence de l'extubation iatrogène sur la survenue d'une pneumonie nosocomiale et la mortalité en réanimation ont été évaluées grâce à un modèle de Cox avec covariables temps dépendant. La survenue de pneumonie nosocomiale était plus fréquente après extubation accidentelle qu'après les autres extubations iatrogènes. L'extubation iatrogène augmente le risque de pneumonie (HR 1.8, IC 95% : 1.15-2.8, p=0.009). Cette augmentation du risque est entièrement due à l'effet des extubations accidentelles sur la survenue des pneumonies (HR= 5.3, IC 95% : 2.8-9.9, $p < 0.001$). L'extubation iatrogène n'influence pas la mortalité, mais elle est associée à une durée plus longue de ventilation mécanique.

Cette étude montre que les extubations iatrogènes sont associées à une certaine morbidité et à un allongement de la durée de séjour. Les extubations accidentelles bien que n'influençant pas directement le risque de décès augmentent le risque de pneumonie nosocomiale (HR : 5.28 IC95% : 2.83-9.89).

Bien que non développés dans l'article, certains problèmes non résolus d'estimation doivent rester en mémoire. Le succès d'extubation programmée est défini par l'absence de réintubation dans les 48 heures chez un survivant. Il existe donc deux relations opposées entre cette variable et la mortalité. (1) si un malade décède encore intubé car trop sévère, il

n'est pas considéré comme en échec d'extubation programmée puisque l'extubation n'a pas été tentée. (2) Le groupe « non exposé » de cette étude comporte donc deux populations très différentes de patients : les patients trop sévères qui ne vont jamais être extubés et qui vont mourir et les malades extubés avec succès qui sortiront de réanimation vivants après un temps de suivi court pour la très grande majorité d'entre eux.

IV Discussion. Perspectives

IV-1 : ajustement, appariement, interaction

Ce travail montre les limites de la mesure du sur-risque de décès attribuables aux évènements nosocomiaux en réanimation.

- La manière dont est porté le diagnostic des infections nosocomiales est très variable d'un centre à l'autre. Cette variabilité influence l'incidence de la maladie et l'estimation du sur-risque.

- Il existe de nombreux facteurs de confusions qu'il faut essayer de prendre tous en compte. Cependant, ces facteurs de confusions sont souvent trop nombreux pour permettre un appariement. Un ajustement sur les facteurs de confusions pourrait être réalisé. La liste des éléments à prendre en compte nécessiterait un échantillon de malades très grand.

- De plus, Il faut probablement prendre en compte les interactions entre facteur de risque et gravité.

Par exemple, l'impact de l'adéquation de l'antibiothérapie initiale sur la mortalité des pneumonies nosocomiales est probablement variable en fonction de la gravité des patients le jour de la pneumonie. L'impact pronostic est probablement faible lorsque le patient est peu grave, un retard thérapeutique de 24 heures n'étant pas préjudiciable. Lorsque, à l'opposé, la gravité des malades est extrême, l'adéquation de

l'antibiothérapie n'empêcherait pas l'issue fatale, et c'est probablement pour les strates de gravité intermédiaire que l'impact de l'adéquation de l'antibiothérapie serait la plus importante[83]. Les résultats préliminaires d'une étude en cours sur la base OUTCOMEREA sur 142 premiers épisodes de pneumonies nosocomiales vont dans ce sens .

IV-2 : Risques compétitifs :

De plus, La multiplicité, la simultanéité et enfin la dépendance des événements en réanimation conduit naturellement à s'intéresser aux modèles à risques compétitifs plus récemment développés. En effet, à l'évidence, les malades de réanimation sont soumis à plusieurs risques simultanément et pour l'instant, aucun des modèles développés dans les revues destinées aux réanimateurs n'ont exploré ce domaine.

Evaluation de l'incidence des pneumonies nosocomiales en fonction de la gravité à l'admission. Prise en compte du décès en réanimation comme un risque compétitif.

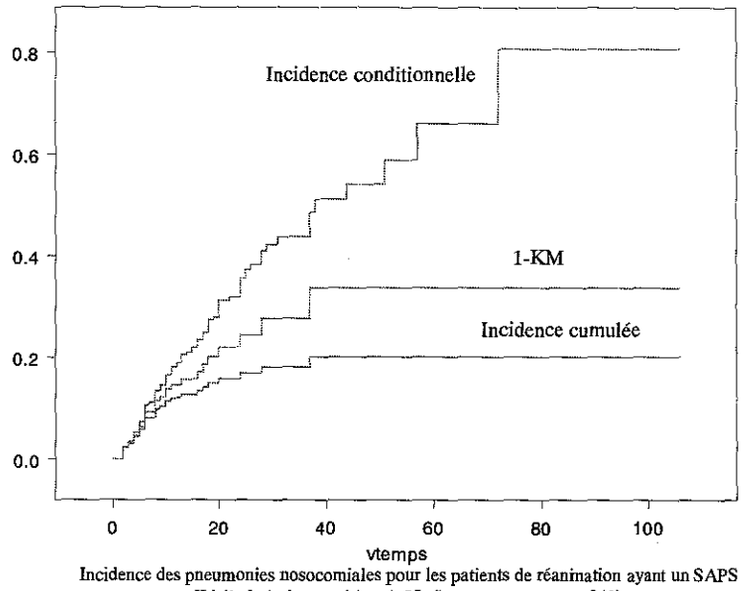
Le sur-risque de décès n'est probablement pas le même en fonction de la gravité des malades à l'admission en réanimation. En effet, les malades les moins graves ont un risque faible d'acquisition de la pneumonie nosocomiale et la pneumonie nosocomiale influence peu leur pronostic vital. A l'opposé, l'impact sur les malades les plus graves d'une pneumonie nosocomiale est probablement faible, compte tenu du risque de décès important inhérent à la maladie sous-jacente.

Il est admis que la gravité initiale mesurée à l'admission en réanimation est, après la durée de ventilation mécanique, le facteur de risque principal des pneumonies nosocomiales. Cependant, ce résultat a été obtenu sur des études de cohorte utilisant des modèles de régression logistique ou sur des études utilisant des modèles de survie classique. Or la durée

de ventilation mécanique n'est pas corrélée linéairement avec la gravité initiale, les durées de ventilation les plus longues étant observées chez les patients de gravité intermédiaire. Si les patients décédés sont censurés, on conçoit volontiers que, lorsque l'on veut évaluer le risque de pneumonie, par strate de gravité à l'admission, la censure par décès soit informative. En effet, lorsque l'on estime la probabilité de survenue d'une pneumonie nosocomiale, on fait l'hypothèse que les sujets décédés avant la pneumonie nosocomiale auraient eu (s'ils étaient restés vivants) la même probabilité de développer une pneumonie que le reste de l'échantillon. De même, après extubation, le risque d'acquisition d'une pneumonie nosocomiale est diminué d'un facteur 10 à 100. Il n'y a donc pas d'indépendance entre la censure (décès, extubation ou sortie vivant du service) et la pneumonie nosocomiale.

En réanimation, si l'on s'intéresse au risque d'acquisition d'une pneumonie nosocomiale, le décès précoce du patient survenant avant la pneumonie est donc un risque compétitif dans l'étude de la survenue d'une pneumonie. Lorsque l'on étudie l'événement « acquisition d'une pneumonie », la censure des patients au décès ou à la sortie vivant de réanimation ignore cette compétition (la population des malades n'étant supposée être soumise qu'au seul risque de pneumonie). Il serait préférable d'estimer la survenue de l'événement « acquisition d'une pneumonie nosocomiale » dans une population soumise à plusieurs risques en compétition (pneumonie, décès avant pneumonie).

Deux mesures probabilistes sont utilisables dans ce contexte de compétition : (1) incidence cumulée, i.e., la probabilité marginale d'acquisition d'une pneumonie au temps t et (2) la probabilité d'acquisition d'une pneumonie nosocomiale au temps t conditionnellement au fait que le patient n'est pas décédé en t. La figure 4 présente une illustration sur un exemple des estimations de ces deux fonctions (comparativement à celle obtenue à partir de l'estimateur de Kaplan Meier).



Incidence des pneumonies nosocomiales pour les patients de réanimation ayant un SAPS II à l'admission supérieur à 55. (base outcomerea, n=249)

Figure 4 : Comparaison des différentes approches de modélisation de l'incidence de pneumonie nosocomiale en fonction de la prise ou non de la compétition

Les perspectives de recherche sont les suivantes.

But : Vérifier si la gravité initiale est un facteur de risque de pneumonie nosocomiale chez les patients ventilés, en comparant les résultats obtenus avec des modèles de survie classiques (en censurant les patients à l'extubation ou au décès) et ceux obtenus avec des modèles prenant le décès et/ou l'extubation comme un risque compétitif.

Méthodes : Construction d'un modèle pronostique en stratifiant sur la gravité à l'admission telle que mesurée par le score SAPS II et évaluation de la sur-mortalité induite par la pneumonie nosocomiale en introduisant la pneumonie comme une covariable dépendante du temps. Utilisation de modèles à risques proportionnels à risques compétitifs [84]

Les premiers résultats de cette approche montrent que la prise en compte du décès comme risque compétitif influence l'estimation du risque de pneumonie nosocomiale associé à la gravité (tableau 12).

Quatre strates de SAPS II successives sont prédéfinies. La variable est transformée en 3 variables discrètes à 2 classes.

Le modèle de Cox classique est réalisé grâce à la procédure PHREG de SAS, le modèle à risques compétitifs est construit sous SPlus grâce à la procédure cmprsk récemment développée par R Gray[84] (Mathsoft, Seattle, WA).

L'interprétation des résultats est dans ce cas délicate. En effet, en tenant compte de la force de mortalité, le risque de survenue de pneumonie nosocomiale chez les patients les plus graves est significativement diminué par rapport aux catégories de gravité initiale intermédiaire et basse. Cependant, le modèle à risques compétitifs considère que chez les patients décédés, le risque de survenue de pneumonie est nul, et décrit la réalité observée. L'interprétation de ce résultat pour le praticien hospitalier est difficile et doit être relative dans la mesure où effectivement ces résultats ne sont interprétables que dans une population soumise à deux risques (pneumonie, décès avant pneumonie). Ainsi, les malades les plus graves développent effectivement moins de pneumonie nosocomiale que les malades moins sévères (HR= *0.64, IC à 95% : 0.42-0.97)*, mais par l'intermédiaire d'une augmentation de leur risque de décès avant pneumonie (HR= *3.41 , IC à 95% : 2.28-5.12)*).

Tableau 13 : Comparaison de l'estimation du sur-risque de pneumonie nosocomiale associé à la catégorie de SAPS II selon la prise en compte du décès avant pneumonie comme un risque compétitif de l'événement d'intérêt

	Nb pneumonie/nb Décès	*Hazard ratio (IC95) pneumonie*	*p*	*Hazard ratio (IC95) Décès en réanimation*	*p*	*Hazard ratio(IC95) Pneumonie Compétitif**	*p*	*Hazard ratio(IC95) Décès Compétitif**	*p*
SAPS II<39 (N=308)	*47/43*	*1*		*1*		*1*		*1*	
38<SAPSII<49 (n=213)	*44/61*	*1.108 (0.74-1.67)*	*0.62*	*1.60 (1.09-2.37)*	*0.02*	*1.055(0.70-1.59)*	*0.79*	*1.52 (0.95-2.47)*	*0.072*
48<SAPSII<58 (n=171)	*39/57*	*1.321 (0.87-2.00)*	*0.19*	*1.95 (1.31-2.90)*	*0.0009*	*1.16(0.77-1.73)*	*0.49*	*1.96 (1.21-3.16)*	*0.005*
SAPSII >57 (n=253)	*41/131*	*0.77(0.51-1.17)*	*0.21*	*2.49 (1.76-3.50)*	$<10^{-4}$	*0.64(0.42-0.97)*	*0.04*	*3.41 (2.28-5.12)*	$<10^{-4}$

(*) prise en compte du décès et de la pneumonie comme risque compétitif

Dans l'exemple ci dessus, nous avons vu comment le modèle à risques compétitifs modifie grandement les estimations des covariables du modèle de Cox (tableau 13). Afin d'interpréter les résultats de ce type d'analyse, il apparaît donc fondamental de présenter les probabilités de tous les événements en compétition. [85] Si l'on s'intéresse à l'effet de la gravité à l'admission sur le risque de survenue d'une pneumonie, l'utilisation d'un modèle à risques compétitifs peut être très délicat d'interprétation si la gravité affecte aussi le risque en compétition (ici le risque de décès).[85]

Autres approches : Une autre approche pourraient être d'utiliser la probabilité conditionnelle d'événement au cours du temps. Cette fonction représente la probabilité pour un sujet de présenter un événement j au temps t sachant qu'il n'a pas présenté un événement k au temps t (Proba (j|non k)).

Si R_j et R_k sont les deux risques en compétition, la distribution de probabilité conditionnelle de R_j est donnée par :

$$CPR_j(t) = \Pr\left[R_j \text{au temps t}\left(1 - \Pr\left(R_k \text{au temps t}\right)\right)\right] = Q_{j\text{-}KM} / \left[1 - Q_{k\text{-}KM}(t)\right]$$

Intuitivement, si le modèle est destiné à déterminer les facteurs de risque de pneumonie nosocomiale pour une utilisation quotidienne, la prise en compte des malades conditionnellement au fait qu'ils soient vivants serait plus logique.

IV-3 Applications des résultats – indicateurs de qualité - Performances

Si les modèles conditionnels paraissent mieux adaptés à la prédiction individuelle pour répondre à la question : « mon malade est t il à risque de présenter une pneumopathie nosocomiale? » les modèles à risque cumulés sont probablement plus utiles en santé publique pour modéliser le risque d'acquisition de pneumonie nosocomiale en fonction du type de population soigné. Les comités de lutte contre l'infection nosocomiale nationaux (C-Clin Paris Nord : Groupe REACAT http://www.jussieu.fr/cclin/reanimation.html) ou

internationaux comme HELICS (Hospital in Europe Link for infection control through surveillance http://helics.univ-lyon1.fr) réfléchissent à la réalisation de scores composites qui permettrait d'utiliser la pneumonie nosocomiale ou d'autres évènements iatrogènes comme indicateur de résultats dans les unités de soins intensifs. Des modèles logistiques ont ainsi été proposés. Les modèles multivariés pour données censurées à risque compétitifs sur le même principe que celui montré précédemment pourraient permettre de prendre en compte à la fois la gravité initiale et la durée d'exposition au risque pour estimer cette mesure. Ce type d'ajustement, associé à une meilleure définition de l'infection, à une homogénéisation de la prise en charge, pourrait permettre d'utiliser l'infection nosocomiale pour l'évaluation de la performance (ou benchmarking) des unités.

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ANNEXE 1

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ORIGINAL

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Accuracy of a composite score using daily SAPS II and LOD scores for predicting hospital mortality in ICU patients hospitalized for more than 72 h

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Abstract In most databases used to build general severity scores the median duration of intensive care unit (ICU) stay is less than 3 days. Consequently, these scores are not the most appropriate tools for measuring prognosis in studies dealing with ICU patients hospitalized for more than 72 h.
Purpose: To develop a new prognostic model based on a general severity score (SAPS II), an organ dysfunction score (LOD) and evolution of both scores during the first 3 days of ICU stay.
Design: Prospective multicenter study.
Setting: Twenty-eight intensive care units (ICUs) in France.
Patients: A training data-set was created with four ICUs during an 18-month period (893 patients). Seventy percent of the patients were medical (628) aged 66 years. The median SAPS II was 38. The ICU and hospital mortality rates were 22.7 % and 30 %, respectively. Forty-seven percent (420 patients) were transferred from hospital wards. In this population, the calibration (Hosmer-Lemeshow chi-square: 37.4, $P = 0.001$) and the discrimination [area under the ROC curves: 0.744 (95 % CI: 0.714–0.773)] of the original SAPS II were relatively poor. A validation data set was created with a random panel of 24 French ICUs during March 1999 (312 patients).
Measurements and main results: The LOD and SAPS II scores were calculated during the first (SAPS1, LOD1), second (SAPS2, LOD2), and third (SAPS3, LOD3) calendar days. The LOD and SAPS scores alterations were assigned the value "1" when scores increased with time and "0" otherwise. A multivariable logistic regression model was used to select variables measured during the first three calendar days, and independently associated with death. Selected variables were: SAPS II at admission [OR: 1.04 (95 % CI: 1.027–1.053) per point], LOD [OR: 1.16 (95 % CI: 1.085–1.253) per point], transfer from ward [OR: 1.74 (95 % CI: 1.25–2.42)], as well as SAPS3-SAPS2 alterations [OR: 1.516 (95 % CI: 1.04–2.22)], and LOD3-LOD2 alterations [OR: 2.00 (95 % CI: 1.29–3.11)]. The final model has good calibration and discrimination properties in the training data set [area under the ROC curve: 0.794 (95 % CI: 0.766–0.820), Hosmer-Lemeshow C statistic: 5.56, $P = 0.7$]. In the validation data set, the model maintained good accuracy [area under the ROC curve: 0.826 (95 % CI: 0.780–0.867), Hosmer-Lemeshow C statistic: 7.14, $P = 0.5$].

Conclusions: The new model using SAPS II and LOD and their evolution during the first calendar days has good discrimination and calibration properties. We propose its use for benchmarking and evaluating the over-risk of death associated with ICU-acquired nosocomial infections.

Introduction

General severity scores such as SAPS II [1], APACHE II [2] or MPM24 [3] have been developed for use at specific time periods during the ICU stay. They measure severity of illness using data collected during the first 24 h after admission to the ICU. These models have been developed in consecutive ICU patients with a relatively short length of stay in the ICU.

Severity adjustment is considered important to ensure the comparability of different groups. In observational studies on outcomes (mortality, complication, length-of-stay) severity scores are mainly used to control for differences in patients' risk profiles. At time, these general severity scores have been used for specific subgroups of ICU patients and/or for time periods different to the one for which they were developed. For example, studies dealing with the over-risk of death of nosocomial events have used either SAPS II [4], MPMII [8] or Apache II/III [5, 6, 7] for adjustment and/or matching. However, only severity of illness at admission in the ICU has been used in most studies. This kind of general severity score should be questioned because it has been built on general ICU populations and not on populations exposed to the risk of nosocomial events (i.e., hospitalized for at least 72 h).

The accuracy of prognostic systems is generally assessed by measuring how well the model distinguishes patients who will die from patients who will survive (discrimination) and the degree of correspondence between observed and predicted mortality (calibration) across the entire range of risks and within subgroups of patients.

In fact, the accuracy of prediction of these general scores is maintained at an acceptable level only in patients who stay in the ICU for a short period of time [9, 10]. The progressive decrease in discrimination power is probably explained in part by the fact that the prognosis of ICU patients changes over time if their clinical condition becomes either more complex or with no or partial response to treatment. In the extreme case, general severity scores measured on admission do not remain associated with prognosis of patients with ICU-acquired nosocomial infections who stay in the ICU for a long time [7, 8, 11]. To measure the over-risk of death induced by nosocomial infections, which, by definition, occur after 72 h of stay in the ICU, we need to use prognostic models built on ICU patients hospitalized at least during that period of time.

In an attempt to improve the prognostic value of severity scores after 3 days of ICU stay, Lemeshow et al. developed MPM 72 [10], a score based on the recalibration of the MPMII [3] using information ascertained at admission and clinical and biological variables assessed during the third ICU day. However, the predictive accuracy of the MPMII was worse at 72 h (area under the ROC curve, 0.752) as compared with 24 h (area under the ROC curve, 0.836) probably because this model did not take into account the evolution of patients until admission [12].

This model, not widely used in France, is, unlike the SAPS II model, primarily based on conditions, and changes from the diagnosis at admission and other case-mix issues could lead to subsequent variations of its performance [13].

The purpose of our study was to develop a new tool which can be used for benchmarking and adjusting the over-risk of death associated with ICU-acquired infection and other ICU-acquired iatrogenic events. For purposes of data reduction, improvement of reliability, and ease of use, we decided to introduce severity indices previously created by others (namely SAPS II and LOD) and already measured in many French ICUs.

Methods

This cohort study was conducted prospectively during an 18-month period within the medical and surgical ICUs of four university-affiliated teaching hospitals: one medical ICU in Hôpital Louis Mourier (Colombes, France), two medical and surgical ICUs in Hôpital Saint Joseph (Paris, France), and Hôpital Avicenne (Bobigny, France), and one surgical ICU in Hôpital Antoine Béclère (Clamart, France). All patients over 16 years of age and hospitalized in the ICU for more than 48 h were entered in the database. For the purpose of this study, we used data collected for patients hospitalized for at least four calendar days in the ICU.

Data collection and baseline data

We recorded prospectively clinical, biological, and therapeutic data from the day of admission to ICU discharge. The investigators were closely involved in the database setting. All codes and definitions were created prior to the study start. Report forms were completed by senior physicians and were all reviewed by another investigator before computation. Using the keyed data, the Simplified Acute Physiologic Score (SAPS II) [1] and the LOD score [14] were computed. The chronic health status, assessed using the Knaus classification [2], was also recorded, as well as the diagnosis and the main symptoms at admission. Transfer from ward was defined as an acute-bed-hospital stay of more than 24 h before ICU admission [15].

We then created a second external validation set. We randomly selected 30 ICUs from around France. The multi-stage randomization of the units was performed according to the proportion of

ICUs from university hospitals, general hospitals or private clinics and to the proportion of medical surgical or medical-surgical ICUs in France. Selected ICUs had to enroll a maximum of twenty consecutive patients hospitalized for at least four calendar days and admitted to the ICU in March 1999. Twenty-four ICUs finally agreed to participate to the validation set creation. The same data were recorded prospectively by the centers for their consecutive patients. Again, another investigator reviewed all the report forms before their computation. An audit was performed by the study monitors of a clinical research organization on a random basis of 10 % of the patients in each ICU.

There were no missing clinical data. According to SAPS II and LOD definitions, missing initial biological data were treated as a normal value. To calculate daily severity scores, missing values were scored as zero when biological data were not estimated at any time. In other cases, missing biological parameters were assumed to be unchanged.

Statistical analysis

Model building

SAPS II and LOD scores were measured by the investigators as previously reported [1, 14]. SAPS II and LOD at day 1, day 2, and day 3 were computed using clinical and biological data recorded during each calendar day in the training data set.

Variables associated with death were selected using Fisher's exact test or the Mann-Whitney test.

All variables were introduced as dummy variables except SAPS II and LOD scores at admission (after checking for log-linearity assumption). The McCabe score was not introduced into the model because of poor inter-observer reproducibility. Score alterations rather than daily scores were introduced in the model at the first step to avoid overfitting. Only the directions of changes were included on the basis of the non-parametric modeling using generalized additive models [16]. According to the plot of the estimated functions for each score alteration using smoothing splines, the direction of change was the most important predictor to delineate two groups of interest (low- and high-risk groups). Alteration of severity scores took the value "1" when scores increased and the value "0" otherwise.

As the ICU population changed over time with an increasing number of patients with chronic illnesses, the latter parameter was also introduced into the initial full model. Chronic illness was either encoded as a binary covariate (presence or absence, one or more than one) or by introducing separately each chronic illness as dummy variables. The best model was chosen by taking the lower value of the Akaikes information criterion [17]. Pooled interaction tests were performed to check for the additivity assumption [18].

A multivariable logistic regression model with a stepwise selection procedure was used to select variables, measured during the first three calendar days, independently associated with hospital death. Only significant variables in the univariate analysis were introduced into the model at the first step.

Our primary assessment of model performance was the goodness of fit of the models on the training data set. Goodness of fit was evaluated by the Hosmer-Lemeshow C statistic, and calibration curves [19]. Lower C values and higher P values are associated with a better fit. A good fit was defined as $P > 0.05$ for the C statistic. The calibration curves of actual vs predicted mortality across deciles of predicted probabilities of death provide a visual depiction of the model calibration. We also assessed the model's discrimination (the ability of the model to separate survivors and non-survivors) using the receiver operating characteristics (ROC) area under the curve (AUC). A ROC-AUC of 1 is a perfect discrimination and a ROC-AUC of 0.5 is random chance. Comparisons between ROC-AUC were performed using Hanley and McNeil's method [20].

Model validation

Internal validation on the training data-set was performed by bootstrapping, which, by taking a large number (500 independent replicates) of samples with the replacement from the original one, provides nearly unbiased estimates of predictive accuracy. External validation was performed using the second data set and using the same tools.

Eventually, MPM72 was measured using clinical and biological data of the third calendar day [10] and was compared to the final model.

Results

Training and validation data sets

Eight hundred and ninety-three (893) patients hospitalized for at least four calendar days were entered in the training data set. Three hundred and twelve (312) patients from 24 ICUs were entered in the external validation data set.

Case-mixes of the training and the validation cohorts are shown in Table 1. The training and validation cohorts were statistically different in term of diagnosis, rate of patients transferred from hospital ward, and evolution of SAPS II and LOD during the first 3 days of ICU course.

Variables separately associated with hospital mortality (Table 2) were introduced in a multivariable model (i.e., SAPS II, LOD, chronic illness, transfer from ward, LOD1-LOD2 alterations, LOD2-LOD3 alterations, SAPS1-SAPS2 alterations, and SAPS2-SAPS3 alterations).

In the first model, chronic illness was introduced as a dummy variable and, in the second one, each chronic illnesses were introduced separately.

In the last step of the stepwise selection procedure at the 5 % level in the first model, the SAPS II score and LOD score at admission remained associated with prognosis as well as the alteration of severity scores (Table 3). Moreover, transfer from hospital ward [21, 22] and chronic illness remained related to death [21].

When chronic illnesses were introduced separately, only hepatic disease [OR: 4.34 (95 % CI: 2.45–7.7)], cardiac disease [OR: 1.67 (95 % CI: 1.03–2.70)], and immunosuppression [OR: 2.07 (95 % CI: 1.31–3.27)] were associated with death, whereas renal and pulmonary chronic diseases were not. The other variables remained in the final model. The Akaike criterion was higher in the second model (AIC = 1113.2 vs AIC = 1105.2). Consequently, the first model was retained.

Table 1 Training and validation cohort characteristics. Results are expressed as median (25^{th}–75^{th} percentiles) or number (%) for quantitative and qualitative variables, respectively

	Training data set ($n = 893$)	Validation data set ($n = 312$)	P value[b]
Symptom at ICU admission			
Multi-system organ failure	30 (3)	8 (3)	0.3
Septic shock	70 (8)	23 (7)	0.6
Other shock	92 (11.5)	32 (11)	0.6
Respiratory failure	310 (34.5)	92 (30)	0.09
COPD exacerbation	75 (8)	17 (5.5)	0.1
Renal failure	54 (6)	9 (3)	0.04
Coma	115 (13)	31 (10)	0.2
Trauma	17 (2)	25 (8)	$< 10^{-4}$
Scheduled surgery	37 (4)	28 (9)	0.002
Other	93 (10)	44 (14)	0.08
Medical	628 (70)	193 (61.7)	0.02
Scheduled surgery	83 (9)	40 (12.9)	
Emergency surgery	182 (21)	79 (25.4)	
Age	66 (49–75)	64 (50–76)	0.1
Transfer from ward	420 (47)	176 (56)	0.005
Chronic illness	428 (48)	143 (46)	0.4
Hepatic	72 (8.1)	15 (4.8)	0.06
Pulmonary	174 (19.5)	65 (20.8)	0.7
Cardiac	100 (14.5)	43 (13.8)	0.5
Renal	14 (1.6)	10 (3)	0.1
Immunosuppression	122 (13.7)	39 (12.6)	0.6
More than one	61 (6.8)	32 (10)	
McCabe score			
Nonfatal	473 (53)	186 (60)	0.08
Fatal < 5 years	317 (35.5)	95 (30.7)	
Fatal < 1 year	55 (11.5)	29 (9.3)	
SAPS admission	38 (28–52)	36.5 (27–50)	0.23
LOD admission	5 (2–7)	5 (2–6)	0.18
ICU stay (days)	7 (7–14)	7 (4–14)	0.7
Hospital stay (days)	22 (12–42)	23 (13–42)	0.8
SAPS day 1	35 (26–45)	37 (29–47)	0.01
SAPS day 2	35 (25–45)	37 (27–47)	0.03
SAPS day 3	33 (23–44)	37 (26–46)	0.03
LOD day 1	5 (2–7)	4 (3–6)	0.01
LOD day 2	5 (3–7)	4 (3–6)	0.002
LOD day 3	4 (2–7)	4 (2–6)	0.006
SAPS3-SAPS2 alteration[a]	280 (31.4)	106 (34)	0.44
LOD3-LOD2 alteration[a]	178 (19.9)	66 (21.2)	0.04
ICU deaths	203 (22.7)	70 (22.5)	0.9
Hospital deaths	268 (30)	84 (27)	0.3

[a] Alteration of severity scores took the value "1" when scores increased and the value "0" otherwise

[b] Fisher's exact test or Mann-Whitney test as appropriate

Table 2 Prognostic factors in the training cohort (univariable analyses). Results are expressed as median (25^{th}–75^{th} percentiles) or number (%) for quantitative and qualitative variables, respectively

	Alive ($n = 625$)	Dead ($n = 268$)	P value
Symptom at ICU admission			< 0.0001
Multi-system organ failure	13 (41)	17 (59)	
Septic shock	48 (69)	22 (31)	
Other shock	51 (56)	41 (44)	
Respiratory failure	221 (71)	310 (29)	
COPD exacerbation	60 (80)	75 (20)	
Renal failure	32 (59)	54 (41)	
Coma	73 (63.5)	115 (36.5)	
Scheduled surgery	30 (81)	7 (19)	
Trauma	15 (88)	2 (12)	
Other	82 (88)	11 (12)	
Transfer from ward	268 (63.8)	152 (36.2)	0.0002
Medical	441 (70.2)	187 (29.8)	0.14
Scheduled surgery	65 (78.3)	18 (21.7)	
Emergency surgery	119 (65.4)	63 (34.6)	
Age	64 (45–73)	70 (57–77)	10^{-4}
Chronic illness	257 (41)	171 (63.8)	$< 10^{-5}$
Hepatic	31 (43)	55 (32)	$< 10^{-5}$
Pulmonary	119 (68)	39 (39)	0.6
Cardiac	61 (61)	4 (29)	0.05
Renal	10 (71)	54 (44)	1
Immunosuppression	68 (56)	54 (44)	0.0004
More than one	36 (59)	25 (41)	0.06
McCabe score			$< 10^{-4}$
Non-fatal	389 (82)	84 (17.7)	
Fatal < 5 years	188 (59.3)	129 (40.7)	
Fatal < 1 year	48 (46.6)	55 (53.4)	
SAPS admission	35 (25–47)	51 (37–63)	$< 10^{-4}$
LOD admission	4 (2–7)	6 (4–8)	$< 10^{-4}$
Age	64 (45–73)	70 (57–77)	$< 10^{-4}$
ICU stay (days)	7 (4–11)	11 (6–19)	$< 10^{-4}$
Hospital stay (days)	24 (15–44)	18 (10–42)	0.002
SAPS day 1	33 (23–42)	41 (51–32)	$< 10^{-4}$
SAPS day 2	31 (21–41)	45 (35–57)	$< 10^{-4}$
SAPS day 3	29 (20–39)	43 (35–58)	$< 10^{-4}$
LOD day 1	4 (2–7)	6 (4–8)	$< 10^{-4}$
LOD day 2	4 (2–7)	7 (5–9)	$< 10^{-4}$
LOD day 3	4 (2–6)	7 (4–8)	$< 10^{-4}$
LOD1-LOD2 alteration[a]*	182 (29)	108 (40)	0.002
SAPS1-SAPS2 alteration[a]*	259 (41)	149 (55)	0.0002
LOD2-LOD3 alteration[a]*	103 (16.5)	75 (28)	0.0002
SAPS2-SAPS3 alteration[a]*	176 (19.7)	104 (38.8)	0.003

[a] Alteration of severity scores took the value "1" when scores increased, and the value "0" otherwise

The overall model calibration was good (training database: goodness of fit statistic = 5.56 with 8 *df*, $P = 0.70$) (Fig. 1). The area under the ROC curve (AUC model = 0.794, 95% confidence interval = 0.766–0.820) was improved as compared to the AUC of SAPS II (area under the ROC curve for SAPS II = 0.744, 95% confidence interval = 0.714– 0.773, $P < 10^{-4}$) (Fig. 2) but remained too imperfect to make individual predictions (concordance of predicted probabilities and observed responses: 75.5% applying a decision criterion of 50%, in 80.5% of the pairs formed by a survivor and a non-survivor patient; the surviving patient had a smaller probability of dying than the patient that did not survive).

In the external validation data set, the model remained well calibrated (goodness of fit statistic = 7.14 with 8 *df*, $P = 0.55$). The discrimination of the model in the external data set was good (area under the ROC

Table 3 Results of the logistic regression (training cohort, $n = 893$, 268 hospital deaths)

	Parameter estimate	Odds ratio 95% CI	P value (Wald)	Odds ratio 95% CI (Bootstrap)
Intercept	–4.44		0.0001	
Transfer from ward (0/1)	0.5543	1.74 (1.25–2.42)	0.001	(1.253–2.453)
LOD at admission	0.1536	1.16 (1.085–1.253)	< 0.0001	(1.093–1.276)
SAPS II admission	0.0388	1.04 (1.027–1.053)	< 0.0001	(1.026–1.053)
Chronic illness (0/1)	0.8507	2.34 (1.677–3.269)	< 0.0001	(1.622–3.296)
SAPS2-SAPS3 alteration	0.4161	1.516 (1.04–2.22)	0.032	(1.055–2.373)
LOD2-LOD3 alteration	0.6940	2.00 (1.29–3.11)	0.0002	(1.292–3.019)

To compute the probability of hospital mortality:
(1) compute the logit:
Logit = (–4.44) + 0.5543 (Transfer) + 0.1536 (LOD) + 0.0388 (SAPS II) + 0.8507 (Chronic illness) + 0.4161 (SAPS2-SAPS3 alteration) + 0.6940 (LOD2-LOD3 alteration);
(2) calculate the probability of hospital mortality [P(death)]:
$P(\text{death}) = (e^{\text{Logit}})/(1+e^{\text{Logit}})$ where $e = 2.7182818$ (the base of the natural logarithm).
An Excel^{R} 4.0 calculation file is available on http://www.outcomerea.org

Table 4 Calibration and discrimination of the final model as compared to SAPS II and MPM 72 in predicting hospital death

	AUC-ROC (95% CI)	Hosmer-Lemeshow C statistic (P value)
Training set		
SAPS II	0.744 (0.714–0.773)	37.4 (0.001)
LOD at admission	0.681 (0.646–0.714)	21.2 (0.01)
MPM72	0.786 (0.757–0.812)	22.3 (0.01)
Final model	0.794 (0.766–0.820)	5.56 (0.70)
Validation set		
SAPS II	0.741 (0.688–0.789)	19.8 (0.02)
LOD at admission	0.725 (0.668–0.777)	32.2 (0.002)
MPM72	0.814 (0.774–0.854)	18.2 (0.03)
Final model	0.826 (0.780–0.867)	7.14 (0.5)

curve = 0.826, Table 4) and very significantly improved ($P < 10^{-4}$) as compared to the original SAPS II or LOD scores (Fig. 3).

The performance of the MPM72 was slightly lower in the training and the external validation data sets with a lower AUC-ROC (Table 4) and a lower fit (goodness of fit statistic = 22.3 with 8 df, $P < 0.01$).

Discussion

Most of the current research with prognostic scoring systems has focused on predictions which use data from the first ICU day. The severity of the acute disease has been associated with a higher risk of nosocomial infection [23, 24] and iatrogenic events [25]. As the severity of the acute disease could have acted as a confounding factor, severity scores have been proposed for risk stratification and quality assurance [26]. Consequently, these scores have been used to adjust the over-risk of death related to nosocomial pneumonia or bacteremia or any other nosocomial events which only occurred after 72 h of ICU stay, by definition [4, 5, 6, 7, 8, 27].

However, these models are not adequate for risk stratification of diseases occurring after 72 h of ICU stay, since they have been built using the overall population of patients. As the ICU stay was less than 3 days for 15–50% of the patients in these data sets [1, 10, 22, 28, 29], the accuracy of these models is poor for patients hospitalized in the ICU for longer periods [9, 10]. The poor calibration and discrimination properties of the original SAPS II in the training and the validation data set of our study corroborate this assumption.

In studies dealing with long-stay ICU patients, severity scores calculated at admission no longer remained related with death. In the study from Ferraris et al. [30] involving 110 patients hospitalized for at least 72 h, the occurrence of nosocomial sepsis, iatrogenic events, and the development of renal failure in the ICU – but not the APACHE II at admission – were associated with ICU outcome.

Similarly, the mean APACHE II score [7] and MPM II score [8] at admission were not different in patients who died and patients with clinical resolution of an episode of nosocomial pneumonia; and initial APACHE II, MODS, and OSF scores were not able to differentiate those patients with ICU-acquired septic shock who died from those who did not [11].

A few data from previous publications indicated that the use of severity scores calculated on the third ICU stay in this population is more accurate. The study from Girou and coworkers illustrated perfectly this finding [27]. She carefully matched, for initial severity of illness (as assessed by APACHE II and age) and duration of exposure to the risk, 42 ICU patients with nosocomial infections with 42 controls. Patients were strictly similar in terms of severity at admission to controls; however, the observed death rate of case-patients was higher than for the controls (58.5% vs 14.6%, $P < 0.001$). Al-

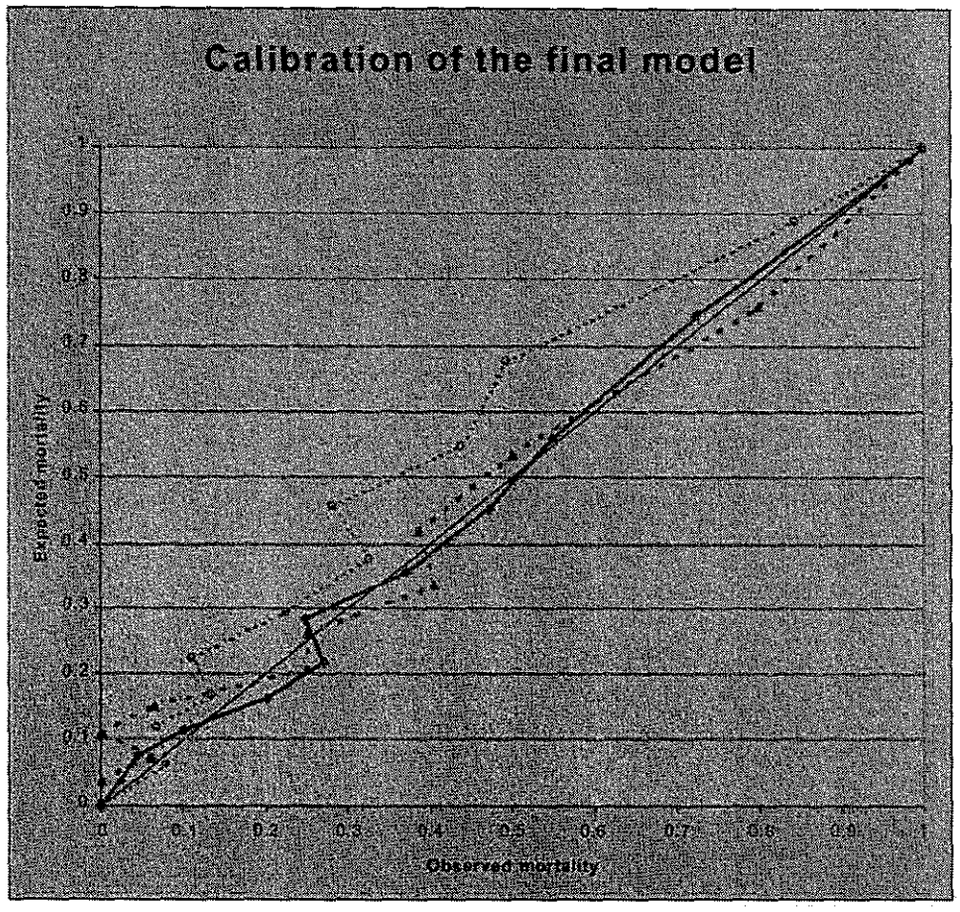

Fig. 1 Observed and predicted mortality of the final model in the training and the external validation data set. Training data set: MPM72: goodness of fit statistic = 22.3 with 8 *df* ($P < 0.01$) (*circle* and *dotted line*); final model: goodness of fit statistic = 5.56 with 8 *df* ($P = 0.70$) *(black line)*. Validation data set: final model: goodness of fit statistic = 7.14 with 8 *df* ($P = 0.5$) (*triangle* and *dotted* line)

though initial severity scores were not able to predict mortality, the APACHE II and the SAPS scores of case-patients calculated on the third day of ICU admission, before nosocomial infection occurred, were significantly higher than those of controls.

Based on these observations, our purpose was to use data available at admission and their evolution during the first 2 days of ICU stay to develop a prognostic model with reasonable calibration and discrimination properties.

In clinical trials, it is important to have properly calibrated models for risk stratification and for measuring severity-adjusted efficacy [31]. Our model discriminates as well as MPM72, with a better fit [10], probably because we took into account the dynamics of the evolution of severity during the first 3 days of ICU stay.

Mortality prediction models are almost always overspecific for the patient samples upon which they were developed, and thus, performance usually deteriorates when models are applied to different population samples [32]. This evaluation is usually performed using cross-validation, dividing the original population randomly into two groups, development and validation. However, this process can be misleading, as the case mix of both groups (development and validation samples) can be expected to be rather similar. In our study we performed two types of validation. We first used the bootstrap method to test the robustness of the beta estimates of the prognostic covariates. Then, we tested the prognostic models in a completely new external population, independent of the original. The external population was composed of the first patients admitted for at least four calendar days in 24 randomly chosen ICUs in France. It differed from the original population for various case-mix issues. Our final model was well fitted in the external validation group, which gave strength to our conclusions. It remains to be evaluated in other countries.

We found that organ dysfunction and general severity scores are not closely linked as that they added prognostic information at ICU admission. This is probably because these two models may not necessarily converge for their probability estimates in individual patients, even though they are using the same outcome measures

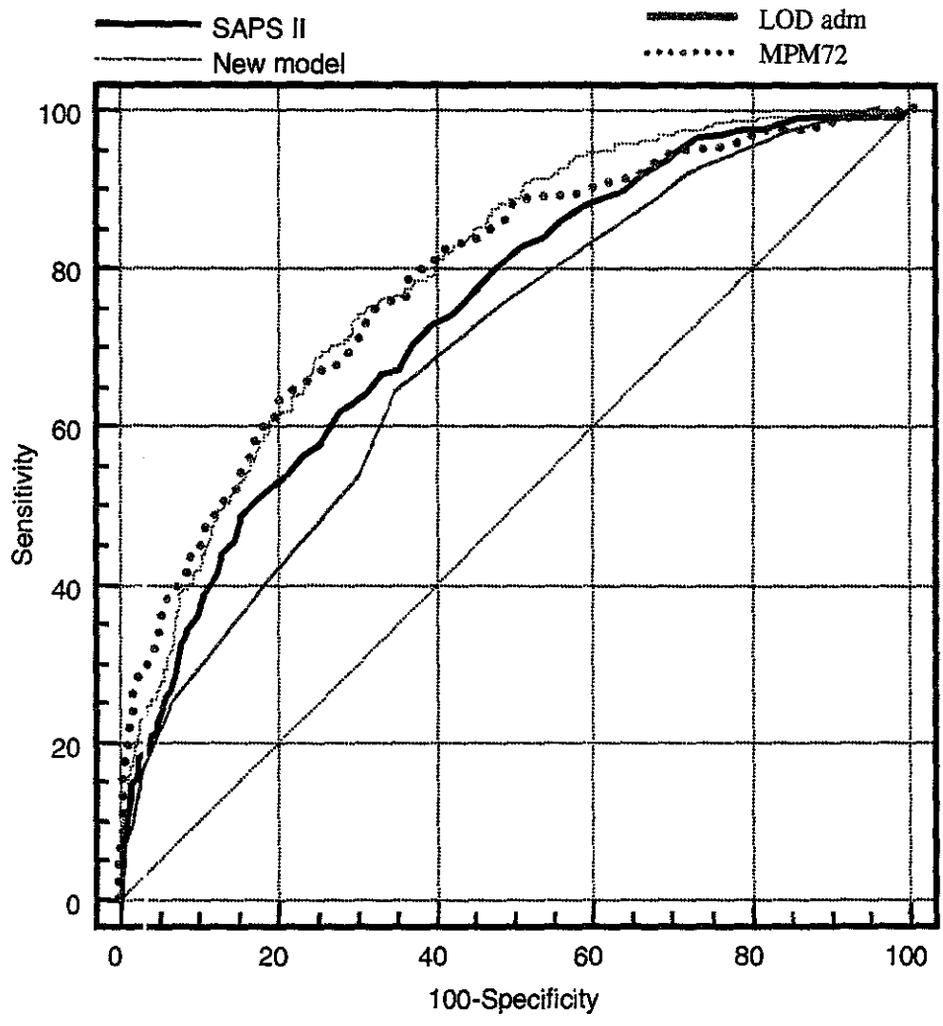

Fig. 2 ROC curve the original SAPS II, LOD score, MPM72, and the final model in the training data set. Original SAPS II: area under the ROC curve = 0.744 (95% confidence interval = 0.714–0.773) *(black line)*. New model: area under the ROC curve = 0.794 (95% confidence interval = 0.766–0.820) *(thin dotted line)*. Area under the ROC curve was significantly improved ($P < 0.0001$) as compared to original LOD *(gray line)* and SAPS II *(black line)* but was not significantly improved as compared to MPM72 *(dotted line)*

[31]. It probably reflects interactions between variables that are used in these general composite scores.

It would have been possible to use a model such as MPM72, built with data obtained at day 3 and without taking into account the evolution between day 1 and day 3. The discrimination of the MPM72 is quite similar to that obtained with our new model in the training population and was slightly lower compared to the validation population. However, MPM72 was not well calibrated and overestimated the probability of death (Fig. 1). However, the main potential interest of the use of the combination of old tools is the potential increase in the reliability of case-mix and physiologic measurements. An important indicator of the quality of a scientific measure is to yield consistent, reproducible results. In France, physicians usually measure the SAPS II score and are familiar with the definitions used in the SAPS II score calculation. It is a strong point for using this strategy in countries already extensively using it, as user variability is improved by the provisions of clear rules and definitions and by training for data collection [33].

Several organ dysfunction scores have been built in the past few years to describe individual organ dysfunction, from mild dysfunction to severe failure, that could be used to measure the evolution of organ dysfunction over time. These systems enable repetitive evaluation and could have been used in the present study. Differences between maximum and initial MODS score [11] or SOFA [28] score also have good accuracy in predicting prognosis of ICU patients. In the paper from Vincent et al. [34], 20% of the survivors increased their total SOFA scores within the first week of ICU stay, while 44% of the non-survivors did not. In this study, the authors concluded that regular repeated scoring enable the patients' condition and disease development to be monitored and better understood. In the same way, the

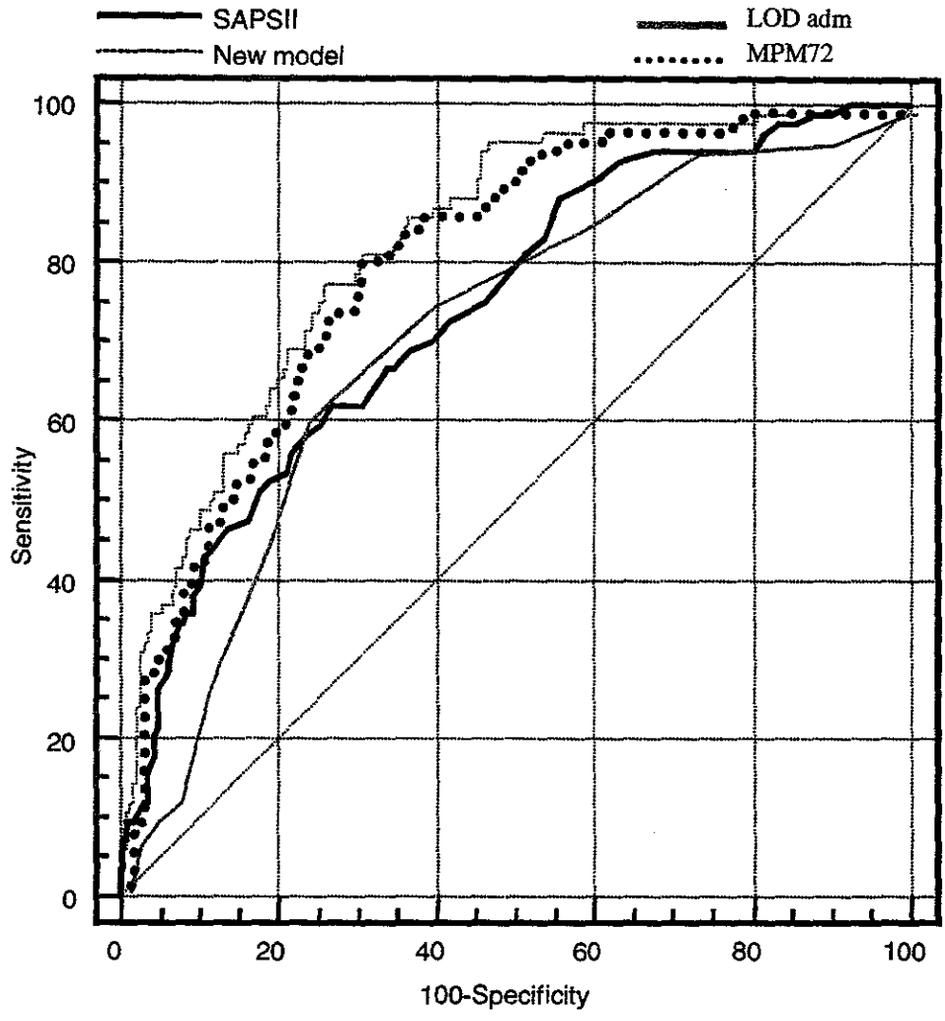

Fig. 3 ROC curve the original SAPS II, LOD score, MPM72, and the final model in the validation external data set. Original SAPS II: area under the ROC curve = 0.741 (95 % confidence interval = 0.688–0.789) *(black line)*. Final model: area under the ROC curve = 0.826 (95 % confidence interval = 0.780–0.867) *(thin dotted line)*. Area under the ROC curve was significantly improved ($P < 0.0001$) as compared to original LOD *(gray line)* and SAPS II *(black line)* but was not significantly improved as compared to MPM72 *(dotted line)*

working group of the European Society of Intensive Care Medicine found that the difference between the maximum SOFA score and the SOFA score calculated at admission is a strong prognostic predictor even after correction for total admission SOFA score [28].

These kinds of organ dysfunction scores are considered as complementary to the general severity scores such as SAPS II. We used the LOD score because it is the sole organ dysfunction score designed for this but also for predicting mortality, although it has not been validated after the first 24 h of ICU stay. However, we previously reported that the evolution of the LOD score from admission was associated with prognosis of ICU patients independently of the appearance of a catheter-related bacteremia [4].

Other multivariate logistic regression equations were developed to create daily estimates of hospital mortality using the APACHE III system [22] and found results very similar to ours. First, the variables entered in the model at admission (i.e., acute physiology score, age, previous hospital stay before ICU admission, and chronic health status) have also been found to contribute to day 3 prediction. Second, the criteria contributing to day 3 prediction were not only the day 3 physiology score (54 %), but also the change in acute physiology score from day 2 to day 3. The discrimination of the day 3 model was excellent and better than those we obtained using the SAPS II and LOD systems. However, even patients who left the ICU on the third day (alive or dead) were entered in this analysis, which artificially led to a better discrimination of the final model. Eventually, the logistic regression equation was not published and a comparison with our model was not possible.

The increase of LOD and SAPS II scores from day 1 to day 2 and from day 2 to day 3 were also associated with the prognosis, and this was observed, independent-

ly of the initial LOD score. However, the amount of variation of the SAPS II and LOD scores showed no log-linear relationship to the risk of death. A decrease of both scores did not provide significant information for the prognosis. On the contrary, an increase in these scores was associated with an increased risk of death. For this reason, instead of the change of score, we used the direction of changes.

When introduced in the multivariable model, day 1 and day 2 changes were not selected. As in the study from Wagner et al. [22], only the more recent changes were retained for the admission variables. This finding probably indicated that the present tendency is more predictive than the full time-course.

In conclusion, our model, which uses very common and easy to ascertain severity and organ dysfunction scores, could be used for adjusting over-risk of death related to ICU-acquired nosocomial events. It might also be useful for mortality benchmarking in ICU patients hospitalized for more than 3 days.

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ANNEXE 2

Calibration and discrimination by daily Logistic Organ Dysfunction scoring comparatively with daily Sequential Organ Failure Assessment scoring for predicting hospital mortality in critically ill patients*

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Objective: The Logistic Organ Dysfunction (LOD) score has been proved effective in evaluating severity during the first day in an intensive care unit but has not been evaluated later. To evaluate attributable mortality related to nosocomial events, organ dysfunction scores that remain accurate throughout the intensive care unit stay are needed. The objective of this study was to evaluate how accurately daily LOD scoring predicts mortality comparatively with daily Sequential Organ Failure Assessment (SOFA) scoring.

Design: Prospective multicenter study.

Setting: Six intensive care units in France.

Patients: A total of 1685 patients with intensive care unit stays longer than 48 hrs were included in this study (511 hospital deaths). Median age was 66 yrs, and median Simplified Acute Physiology Score II at admission was 38. For each patient, a senior physician recorded the variables needed to compute organ dysfunction scores daily throughout the intensive care unit stay.

Interventions: None.

Measurements and Main Results: SOFA and LOD scores were computed daily during the first 7 days. Calibration was evaluated based on goodness-of-fit by the Hosmer-Lemeshow chi-square statistic (lower chi-square values and higher p values indicate better fit) and discrimination based on the receiver operating characteristics (ROC) area under the curve (AUC; a ROC-AUC of 1 indicates faultless discrimination and a ROC-AUC of 0.5 indicates the effects of chance alone). Because calibration of both scores was poor at all time points ($p < .001$), customization was performed using the total score (model 1) or separate introduction of each dysfunction (model 2). The performance of customized LOD and SOFA scores on a given day in predicting mortality was assessed in those patients who spent at least one more calendar day in the intensive care unit. The original LOD and SOFA scores had satisfactory ROC-AUC values (0.720 to 0.766). Internal consistency of both scores was acceptable ($p < 10^{-4}$ for each organ dysfunction). After customization, the original scores calibrated well between days 1 and 7. Discrimination by both scores was better with model 2 (AUC-ROC, 0.729–0.784).

Conclusion: Daily LOD and SOFA scores showed good accuracy and internal consistency, and they could be used to adjust severity for events occurring in the intensive care unit. (Crit Care Med 2002; 30:2003–2013)

KEY WORDS: severity scores; organ dysfunction; organ failure; intensive care unit; critically ill; Logistic Organ Dysfunction; Sequential Organ Failure Assessment; calibration; discrimination; receiver operating characteristic curves; logistic regression; customization

The accuracy of severity scores used to predict mortality in intensive care unit (ICU) patients is generally assessed based on discrimination between survivors and nonsurvivors (discrimination) and on correspondence between observed and predicted mortality (calibration) across the entire range of risk and within patient subgroups. When determined at admission, these severity scores show acceptable accuracy only in patients with brief ICU stays (1–2). They are not well correlated with mortality in patients with long ICU stays, during which nosocomial infections are common (3–5). Furthermore, an important goal is to adjust (match) risk on severity of illness based on severity measurements provided by well-calibrated models used during the ICU stay before the event of interest (6).

Many studies have shown that severity scores computed during the ICU stay were independent predictors of death. In particular, the number of organ system failures on the day of nosocomial infection onset was closely associated with mortality in studies of the attributable probability of mortality induced by catheter-related infections (7–9) or nosocomial pneumonia (4, 10). Moreover, daily severity scores explained a far greater

*See also p. 2151.

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Table 1. Prognostic factors in the training cohort

	Alive (n = 1174)	Dead (n = 511)	p Value
Clinical status at ICU admission			$<10^{-4}$
Multiple system organ failure	28 (2)	36 (7)	
Septic shock	81 (7)	63 (13)	
Other shock	92 (8)	66 (13)	
Respiratory failure	367 (31)	157 (30)	
COPD exacerbation	113 (10)	32 (6)	
Renal failure	59 (5)	33 (6)	
Coma	154 (13)	84 (17)	
Scheduled surgery	125 (11)	24 (5)	
Trauma	23 (2)	3 (0.5)	
Other	132 (11)	13 (2.5)	
Transfer from ward	580 (47)	301 (59)	$<10^{-4}$
Medical	799 (68)	369 (72)	$<10^{-4}$
Scheduled surgery	178 (16.6)	37 (7)	
Emergency surgery	204 (17.4)	109 (21)	
Age	64 (45–73)	70 (57–77)	$<10^{-4}$
Sex			.008
Male	714 (61)	165 (32)	
Female	460 (39)	346 (68)	
Hematologic malignancy	41 (3.5)	45 (8.8)	$<10^{-4}$
Metastatic cancer	65 (5.5)	47 (9.2)	$<10^{-4}$
Chronic illness	462 (39)	321 (62.3)	$<10^{-4}$
Hepatic	50 (4)	51 (10)	$<10^{-4}$
Pulmonary	219 (18)	114 (22)	.08
Cardiovascular	107 (9)	81 (16)	$<10^{-4}$
Renal	11 (1)	18 (4)	.37
Immunosuppression	134 (11)	116 (23)	$<10^{-4}$
More than one	52 (4)	65 (13)	.0006
Mc Cabe score			$<10^{-4}$
Not fatal	693 (59)	157 (31)	
Fatal <5 yrs	391 (33)	249 (49)	
Fatal <1 yr	90 (8)	102 (20)	
SAPS II at admission	35 (25–47)	51 (39–66)	$<10^{-4}$
Age	64 (48–74)	71 (59–78)	$<10^{-4}$
ICU stay, days	6 (4–11)	9 (6–19)	$<10^{-4}$
Hospital stay, days	23 (13–42)	19 (8–43)	$<10^{-4}$

ICU, intensive care unit; COPD, chronic obstructive pulmonary disease; SAPS, Simplified Acute Physiology Score.

Univariable analyses. Results are expressed as median (25th–75th percentiles) or number (%) for quantitative and qualitative variables, respectively. Fisher's exact tests or Mann-Whitney tests were used for statistical analyses.

proportion of the probability of mortality than severity scores at admission (11, 12). A daily organ dysfunction score for risk adjustment or matching would be valuable. However, little is known about the statistical properties of organ dysfunction scores measured throughout the ICU stay (13). The purpose of our study was to evaluate the performance of two organ dysfunction scores (the Logistic Organ Dysfunction [LOD] (14) and the Sequential Organ Failure Assessment [SOFA] (15) scores) computed daily during the first seven ICU days.

METHODS

This cohort study was conducted during a 24-month period in the ICUs of six teaching hospitals in or near Paris, France. Two ICUs were medical (Louis Mourier Hospital, Colombes, and Saint Louis Hospital, Paris), two were medical and surgical (Saint Joseph Hospital, Paris, and Avicenne Hospital, Bobigny), and two were surgical (Antoine Béclère Hospital, Clamart, and Saint Joseph Hospital, Paris). All patients who were >16 yrs old and spent >48 hrs in the participating ICUs were included in the database.

Data Collection and Baseline Data. We prospectively recorded clinical, laboratory, and therapeutic data from ICU admission to ICU discharge. The investigators were closely involved in setting and compiling the database. All codes and definitions were established before data collection. Report forms were completed daily by senior physicians and were reviewed by another investigator before analysis. The data were entered into a com-

Table 2. Performance of the daily Logistic Organ Dysfunction (LOD) score compared with the daily Sequential Organ Failure Assessment (SOFA) score

		LOD Score					SOFA Score				
Day	No. of Deaths (%)	Intercept	β Coefficient (95% CI) (Bootstrap)	AUC-ROC	HLstat (p)	R^2	Intercept	β Coefficient (95% CI) (Bootstrap)	AUC-ROC	HLstat (p)	R^2
1	511 (30.3)	−2.198	0.319 (0.268–0.373)	0.726	10.4 (.16)	.19	−2.18	0.231 (0.203–0.260)	0.720	4.55 (.8)	.19
2	473 (30.1)	−2.27	0.360 (0.268–0.411)	0.742	12.2 (.06)	.22	−2.26	0.258 (0.216–0.287)	0.742	11.1 (.2)	.22
3	428 (32)	−2.22	0.362 (0.309–0.419)	0.752	10.2 (.11)	.23	−2.27	0.267 (0.230–0.302)	0.762	9.94 (.27)	.25
4	387 (34.4)	−2.20	0.377 (0.301–0.449)	0.754	3.9 (.7)	.17	−2.15	0.267 (0.228–0.312)	0.766	10.5 (.23)	.26
5	344 (36.3)	−2.05	0.360 (0.294–0.449)	0.739	7.7 (.4)	.20	−1.94	0.243 (0.203–0.286)	0.746	13.6 (.09)	.23
6	319 (39.3)	−2.20	0.417 (0.329–0.516)	0.756	5.7 (.61)	.26	−2.01	0.282 (0.236–0.349)	0.763	12.2 (.14)	.27
7	294 (42)	−1.92	0.369 (0.289–0.472)	0.736	9.8 (.19)	.22	−1.76	0.271 (0.199–0.295)	0.746	7.3 (.5)	.24

CI, confidence interval; AUC-ROC, area under the curve-receiver operating characteristics; HLstat, Hosmer-Lemeshow statistic.

Scores were calculated on a given calendar day (n), and only patients with intensive care unit stays of at least n + 1 calendar days were included.

No statistically significant differences in discrimination were found between the daily LOD scores and the daily SOFA scores.

Table 3. Distribution of severity levels of organ dysfunctions on days 1, 3, and 7

Organ score	No. of Patients (Hospital Mortality, %)					
	Neurologic	Cardiovascular	Renal	Hematologic	Pulmonary	Hepatic
SOFA						
Day 1						
0	1093 (23)	712 (21)	858 (23)	1042 (26)	734 (24)	1375 (27)
1	245 (36)	423 (30)	315 (28)	313 (31)	100 (23)	148 (43)
2	129 (36)	168 (27)	170 (45)	200 (40)	538 (30)	129 (48)
3	148 (49)	187 (41)	165 (40)	87 (52)	254 (45)	21 (62)
4	70 (74)	195 (57)	177 (44)	43 (42)	59 (64)	12 (50)
Day 3						
0	880 (23)	625 (21)	729 (22)	791 (26)	651 (23)	1064 (28)
1	210 (41)	297 (30)	197 (38)	268 (35)	46 (9)	122 (39)
2	111 (43)	107 (31)	127 (44)	175 (37)	397 (37)	112 (53)
3	87 (54)	145 (47)	101 (52)	73 (64)	208 (50)	25 (56)
4	48 (93)	162 (66)	182 (45)	29 (52)	34 (68)	13 (69)
Day 7						
0	423 (31)	309 (30)	381 (33)	484 (34)	308 (36)	524 (38)
1	139 (50)	188 (42)	75 (44)	97 (45)	21 (24)	60 (43)
2	59 (56)	56 (43)	79 (54)	81 (68)	217 (46)	82 (54)
3	45 (67)	64 (64)	62 (53)	26 (77)	137 (51)	20 (65)
4	34 (91)	83 (72)	103 (59)	12 (75)	17 (53)	14 (93)
LOD						
Day 1						
0	1255 (24)	1152 (23)	403 (18)	1538 (29)	773 (20)	1424 (28)
1	233 (39)	458 (44)	396 (22)	144 (47)	738 (37)	261 (43)
3	127 (49)	68 (59)	777 (40)	3 (66)	174 (49.5)	
5	70 (74)	7 (57)	109 (38)			
Day 3						
0	1024 (25)	1013 (26)	345 (15)	1225 (30)	577 (23)	1144 (29)
1	193 (45)	272 (53)	291 (29)	110 (59)	644 (41)	192 (47)
3	71 (55)	34 (56)	603 (40)	1 (0)	115 (58)	
5	48 (94)	17 (23)	97 (52)			
Day 7						
0	516 (35)	541 (37)	109 (26)	658 (40)	191 (23)	319 (48)
1	112 (52)	134 (57)	159 (36)	42 (71)	436 (49)	75 (60)
3	38 (66)	14 (71)	319 (48)	0 (–)	73 (53)	
5	34 (91)	11 (82)	75 (60)			

SOFA, Sequential Organ Failure Assessment; LOD, Logistic Organ Dysfunction.

The Cochran-Armitage test for trend was highly significant at all severity levels of each organ dysfunction ($p < 10^{-4}$), indicating good internal consistency. The numbers in parentheses indicate the observed hospital mortality for a given organ failure. The maximal value for the hematologic and pulmonary components in the LOD score is 3 and for the hepatological component is 1 (see Appendix).

puter and used to compute the LOD and SOFA scores and the respective contributions of each organ failure (cardiovascular, pulmonary, hematologic, neurologic, renal, and hepatic) to each of the two scores, as described elsewhere (14, 15). We also recorded the diagnosis, main symptoms at admission, and chronic health status assessed using the classification by Knaus et al (16). Transfer from another ward was defined as a stay in an acute bed ward for >24 hrs immediately before ICU admission. ICU and hospital mortality were recorded. There were no missing clinical data. In keeping with published descriptions of the SOFA and LOD, initial missing laboratory test results were recorded as normal. For daily severity score computations, missing values for laboratory tests that were not performed were recorded as normal, and those for laboratory tests done previously were recorded by carrying the last available value forward.

Statistical Analysis. Organ dysfunction scores were computed using clinical and laboratory data recorded on each calendar day. Day 0 was defined as the interval from the time of admission to 8 am on the next day; all other days were calendar days from 8 am to 8 am. The value of daily LOD and SOFA scores on any given day was assessed in patients who spent at least one additional calendar day in the ICU.

To assess internal consistency of the two scores, we evaluated mortality rates associated with involvement of each organ system and with each level of organ failure. Kendall's τ_b correlation coefficient was used to investigate associations among involvements of the six organ systems. Logistic regression was used to create two customized models for each score. Model 1 involved customizing the total score obtained with the original model (first-level customization).

Model 1: Logit organ dysfunction score (Day n) = α_n + (β_n (total score on day n).

When using this strategy of customization, the calibration of the original model does not change, but the calibration improves. In model 2, each organ component of the score was introduced separately (second-level customization).

Model 2: Logit organ dysfunction score (Day n) = α_n + β_n (cardiovascular) + χ_n (pulmonary) + δ_n (neurologic) + ϵ_n (hematologic) + ϕ_n (renal) + γ_n (hepatic).

In model 2, cardiovascular, pulmonary, neurologic, hematologic, renal, and hepatic represent the point assigned to each organ dysfunction in the original model.

Customizing the organ components involves fitting a new logistic regression equa-

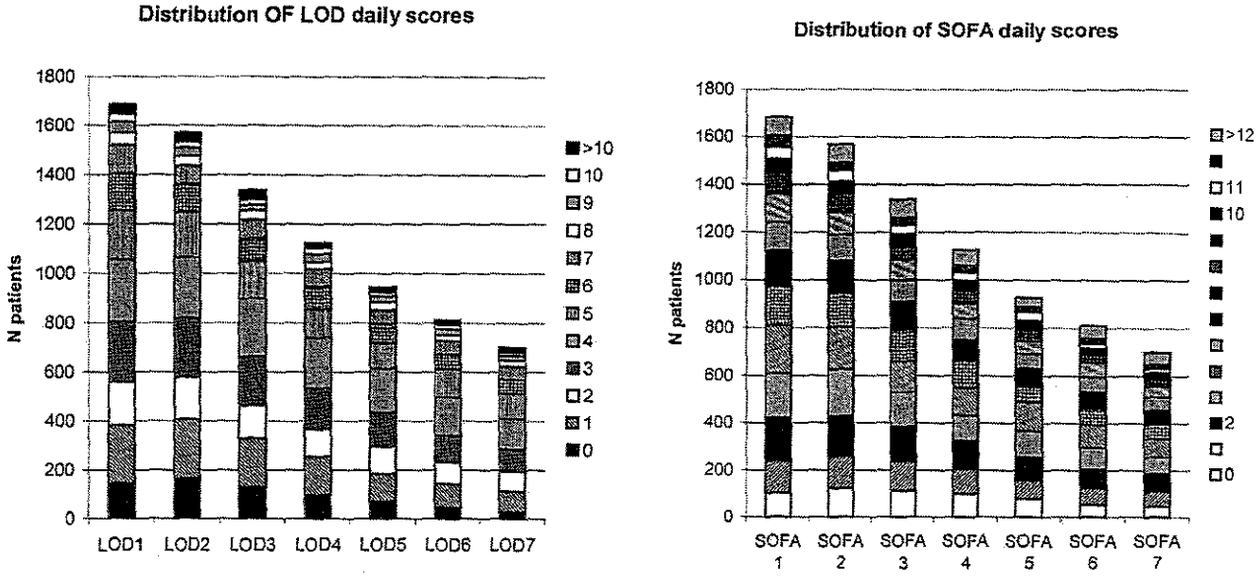

Figure 1. Repartition of patients included in the analyses according to Logistic Organ Dysfunction (*LOD*) and Sequential Organ Failure Assessment (*SOFA*) scores.

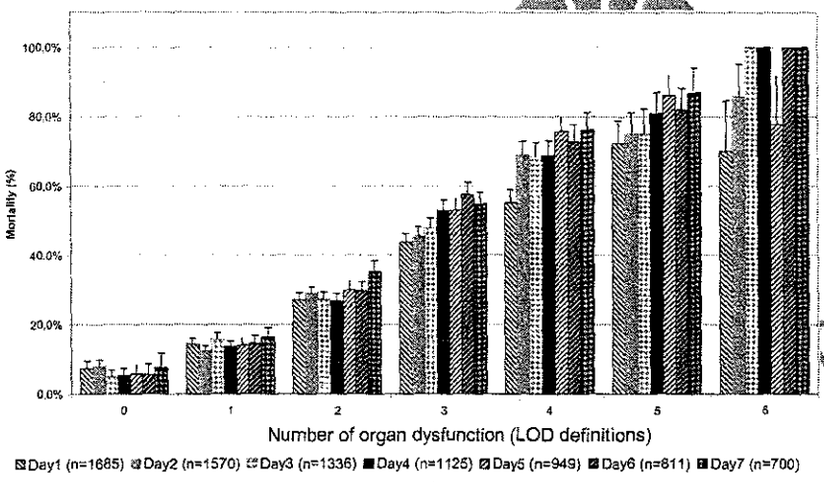

Figure 2. Percentage of deaths according to the number of organ dysfunctions, Logistic Organ Dysfunction (*LOD*) system: mortality rate (%) and number of organ dysfunctions (dysfunction of a given organ is defined as ≥1 points for that organ on days 1–7). The Cochran-Armitage test for trends was highly significant ($p < 10^{-4}$) on all 7 days.

tion with data collected from the specific ICU in which the model will be used so that the customized model contains the same variables as the original model but with coefficients that are unique to a given ICU (17).

We used various tests to evaluate the performance of daily LOD and SOFA scores. Our primary assessment of model performance was goodness-of-fit as evaluated by the Hosmer-Lemeshow statistic and by calibration curves (18). Lower Hosmer-Lemeshow values and higher p values indicate better fit. Good fit was defined as $p > .05$ for the Hosmer-Lemeshow statistic. We also assessed discrimination (the ability of the model to separate survivors and nonsurvivors) using the receiver operating characteristics (ROC) area under the curve (AUC). A ROC-AUC of 1 indicates perfect discrimination, and an ROC-AUC of 0.5 indicates the effects of chance alone. The method of Hanley and McNeil (19) was used to compare ROC-AUC values. Data were analyzed using SAS 8.0 (SAS Institute, Cary, NC) and Medcalc 5.00 (Medcalc, Ghent, Belgium).

Model Validation. Internal validation of the data set was performed by bootstrapping, which involves analyzing a large number (500 independent replicates) of subsamples with replacement from the full sample. Bootstrapping provides nearly unbiased estimates of prediction accuracy.

RESULTS

A total of 1685 patients with ICU stays of >48 hrs were included in the OUTCOMEREA database. Table 1 shows the case mix. Median age was 66 yrs (quartile 1, 51 yrs; quartile 3, 76 yrs). Median ICU stay length was 6 days (quartile 1, 4 days; quartile 3, 14 days). The ICU mortality rate was 22.5%, and the hospital mortality rate was 30.3%. The mean severity profile of patients increased over time, as shown by the increase in observed mortality from 30.3% on day 1 to 40% on day 7 (Table 2). However, the correlations between organ dysfunction scores and ICU length of stay was very poor. The daily LOD or SOFA scores never explained >12.5% of the variance of the ICU length of stay.

According to SOFA definitions, the number of organ dysfunctions on day 1 was 0, 1, 2, 3, or >3 in 6%, 20%, 25%, 23%, and 26% of patients, respectively. Cardiovascular (58%), pulmonary (56.4%), and renal (49%) dysfunctions were more common than hematologic (38%), neurologic (35%), and hepatic (18%) dysfunctions. Similarly, according to the LOD definitions, the number of organ dysfunctions on

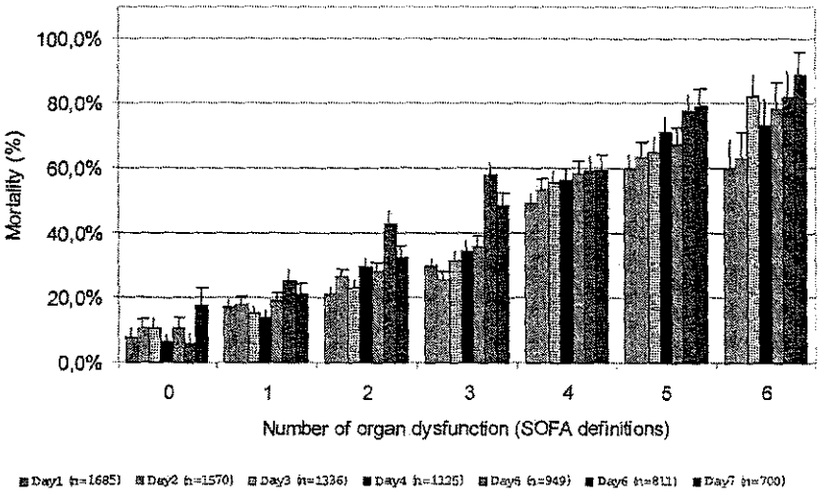

Figure 3. Sequential Organ Failure Assessment (*SOFA*) system: mortality rate (%) and number of organ dysfunctions (dysfunction of a given organ is defined as ≥1 points for that organ) on days 1 to 7. The Cochran-Armitage test for trends was highly significant ($p < 10^{-4}$) on all 7 days.

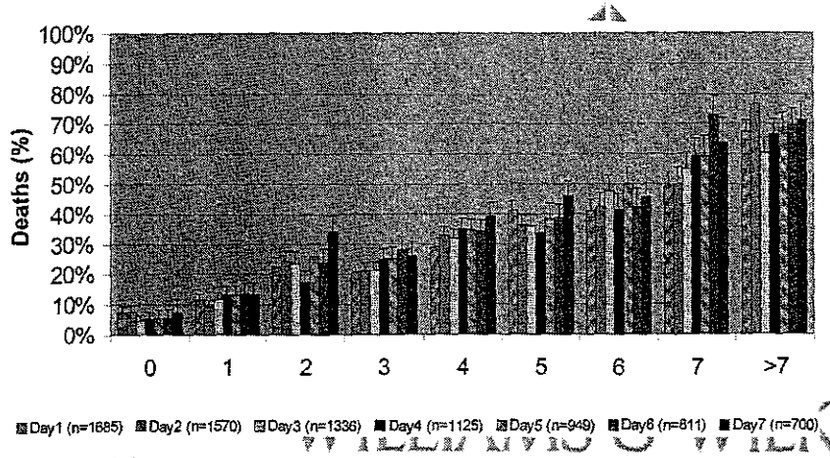

Figure 4. Daily Logistic Organ Dysfunction (*LOD*) scores and hospital mortality. Observed mortality was consistently higher than mortality predicted by the original LOD score, indicating poor fit (Hosmer-Lemeshow chi-square = 221, $p < .001$).

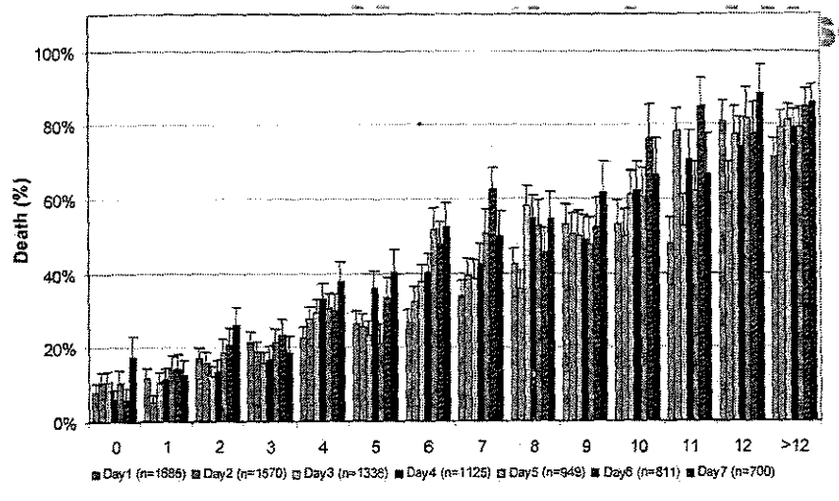

Figure 5. Daily Sequential Organ Failure Assessment (*SOFA*) score and hospital mortality.

day 1 was 0, 1, 2, 3, or >3 in 9%, 25%, 29%, 23%, and 14% of patients, respectively. With the LOD system, renal (78%) and pulmonary (54%) dysfunctions were more common than cardiovascular (32%), neurologic (25%), hepatic (15.5%), and hematologic (9%) dysfunctions. The distribution of patients according to the type and severity level of organ dysfunctions was more homogeneous with the SOFA score than the LOD score, particularly for hematologic dysfunction (level 3) and cardiovascular dysfunction (levels 3 and 5) (Table 3). The number of patients with each LOD daily score are in Figure 1. Hospital mortality rates by number of organ dysfunctions are shown in Figures 2 and 3. They increased with the number of organ dysfunctions by both scoring systems (Table 3, Figs. 4 and 5). The observed mortality at a given SOFA level and, to a lesser extent, a given LOD level increased with the length of ICU stay (Figs. 4 and 5).

LOD scores on days 1, 3, and 7 showed good internal consistency (Table 3). Similar results were obtained with the SOFA system, except that observed hospital mortality related to pulmonary dysfunction did not increase between days 0 and 2 and that observed hospital mortality related to renal dysfunction was similar from day 1 to day 4. Correlation analysis (Kendall's τ_b correlation coefficient) showed strong positive correlations among the six LOD scores for most organ components between day 1 and day 5. Conversely, there were few significant correlations among organ components on days 6 and 7. With the SOFA system, correlation analysis showed strong positive correlations on all days except for pulmonary vs. liver dysfunction on all days and for pulmonary vs. hematologic dysfunction on days 1, 2, and 4.

Discrimination by the LOD and SOFA scores with and without customization by separate introduction of each organ component (model 2) is shown in Tables 2 and 4, respectively. The AUC-ROC values of both uncustomized organ dysfunction scores were very similar, ranging from 0.720 to 0.763. After customization, the range was 0.729–0.784. No significant differences in discrimination were found on any day between the two scores customized using either model. With the LOD score, the improvement in discrimination obtained using model 2 (as compared with model 1) was significant only on days 1, 2, and 3. The

Table 4. Logistic regression models with vital status at hospital discharge as the dependent variable and the organ dysfunction components measured on day n as the explanatory variables

	LOD		SOFA	
Variable	β Estimate	OR (95% CI) (95% CI: Bootstrap)	β Estimate	OR (95% CI) (95% CI: Bootstrap)
Day 1: 511 nonsurvivors/1174 survivors (30.3%)				
Constant	−2.12		−2.16	
Hepatic dysfunction	0.425	1.54 1.14–2.09 1.53 1.17–2.05	0.248	1.28 1.10–1.50 1.29 1.13–1.53
Pulmonary dysfunction	0.285	1.33 1.17–1.51 1.32 1.17–1.50	0.188	1.20 1.10–1.32 1.19 1.11–1.28
Hematologic dysfunction	0.599	1.82 1.28–2.58 1.80 1.31–2.65	0.161	1.17 1.05–1.31 1.17 1.06–1.28
Cardiovascular dysfunction	0.427	1.53 1.32–1.77 1.54 1.31–1.77	0.238	1.28 1.15–1.34 1.24 1.17–1.32
Neurologic dysfunction	0.351	1.42 1.30–1.55 1.41 1.30–1.55	0.400	1.52 1.39–1.67 1.52 1.42–1.65
Renal dysfunction	0.246	1.28 1.18–1.38 1.28 1.11–1.39	0.183	1.20 1.11–1.31 1.20 1.13–1.29
	HLstat: 11, 3 p = .19, AUC: 0.733		HLstat: 11, p = .2, AUC: 0.729	
Day 2: 473 nonsurvivors/1097 survivors (30.1%)				
Constant	−2.17		−2.27	
Hepatic dysfunction	0.486	1.63 1.18–2.27 1.66 1.09–2.29	0.177	1.19 1.03–1.41 1.20 1.04–1.41
Pulmonary dysfunction	0.462	1.59 1.39–1.84 1.61 1.38–1.84	0.210	1.25 1.13–1.37 1.24 1.13–1.37
Hematologic dysfunction	0.465	1.61 1.08–2.37 1.64 1.04–2.57	0.175	1.18 1.06–1.35 1.19 1.06–1.35
Cardiovascular dysfunction	0.383	1.45 1.22–1.73 1.44 1.19–1.76	0.265	1.33 1.18–1.39 1.33 1.17–1.37
Neurologic dysfunction	0.432	1.53 1.38–1.72 1.53 1.38–1.73	0.484	1.67 1.50–1.85 1.66 1.52–1.85
Renal dysfunction	0.240	1.25 1.15–1.35 1.25 1.16–1.36	0.208	1.25 1.15–1.35 1.25 1.16–1.36
	HLstat: 13.5, p = .10, AUC: 0.748		HLstat: 8.3, p = .4, AUC: 0.752	
Day 3: 428 nonsurvivors/908 survivors (32%)				
Constant	−2.18		−2.29	
Hepatic dysfunction	0.533	1.714 1.196–2.458 1.738 1.147–2.469	0.273	1.305 1.112–1.555 1.304 1.098–1.587
Pulmonary dysfunction	0.488	1.629 1.395–1.903 1.637 1.368–1.910	0.275	1.32 1.19–1.46 1.260 1.120–1.400
Hematologic dysfunction	0.704	2.02 1.292–3.102 2.029 1.417–3.189	0.125	1.144 0.999–1.304 1.144 0.987–1.303
Cardiovascular dysfunction	0.137	1.126 0.958–1.323 1.120 0.945–1.365	0.291	1.370 1.218–1.452 1.370 1.210–1.480
Neurologic dysfunction	0.495	1.640 1.448–1.857 1.646 1.475–1.853	0.508	1.620 1.48–1.87 1.740 1.520–1.970
Renal dysfunction	0.279	1.322 1.211–1.443 1.321 1.211–1.448	0.191	1.216 1.113–1.328 1.220 1.090–1.332
	HLstat: 23.3, p = .003, AUC: 0.761		HLstat: 11.3, p = .19, AUC: 0.773	
Day 4: 387 nonsurvivors/738 survivors (34.4%)				
Constant	−2.15		−2.20	
Hepatic dysfunction	0.572	1.772 1.221–2.569 1.806 1.198–2.583	0.223	1.248 1.053–1.482 1.261 1.020–1.490
Pulmonary dysfunction	0.501	1.666 1.418–1.957 1.666 1.465–2.016	0.303	1.34 1.21–1.51 1.310 1.166–1.454
Hematologic dysfunction	0.825	2.295 1.391–3.786 2.410 1.311–4.023	0.196	1.215 1.054–1.402 1.217 1.050–1.420
Cardiovascular dysfunction	0.204	1.60 1.020–1.426 1.219 1.005–1.464	0.308	1.36 1.243–1.503 1.403 1.240–1.520
Neurologic dysfunction	0.460	1.585 1.389–1.810 1.611 1.397–1.853	0.503	1.66 1.51–1.94 1.700 1.510–1.950
Renal dysfunction	0.285	1.33 1.185–1.426 1.307 1.189–1.446	0.137	1.14 1.051–1.267 1.14 1.038–1.274
	HLstat: 11, p = .18, AUC: 0.760		HLstat: 7.3, p = 7.3, p = .5, AUC: 0.779	

Table 4. Continued

Variable	LOD β Estimate	LOD OR (95% CI) (95% CI: Bootstrap)	SOFA β Estimate	SOFA OR (95% CI) (95% CI: Bootstrap)
Day 5: 344 nonsurvivors/605 survivors (36.3%)				
Constant	−1.93		−1.95	
Hepatic dysfunction	0.522	1.719 1.156–2.555	0.157	1.166 0.977–1.391
		1.712 1.167–2.634		1.181 0.966–1.399
Pulmonary dysfunction	0.353	1.434 1.214–1.694	0.142	1.15 1.02–1.30
		1.432 1.223–1.696		1.14 0.979–1.256
Hematologic dysfunction	0.969	2.604 1.515–4.476	0.237	1.278 1.101–1.486
		2.693 1.530–4.760		1.297 1.106–1.484
Cardiovascular dysfunction	0.443	1.524 1.211–1.918	0.329	1.376 1.242–1.524
		1.521 1.158–2.152		1.380 1.230–1.530
Neurologic dysfunction	0.493	1.34 1.403–1.896	0.538	1.748 1.522–2.006
		1.636 1.374–1.987		1.760 1.540–2.030
Renal dysfunction	0.234	1.226 1.113–1.352	0.141	1.157 1.047–1.279
		1.234 1.120–1.342		1.157 1.036–1.293
	HLstat: 13.3, p = .10, AUC: 0.749		HLstat: 14.4, p = .07, AUC: 0.763	
Day 6: 319 nonsurvivors/492 survivors (39.3%)				
Constant	−2.11		−2.01	
Hepatic dysfunction	0.725	2.99 1.382–3.189	0.231	1.270 1.046–1.543
		2.102 1.420–3.346		1.267 1.090–1.550
Pulmonary dysfunction	0.392	1.486 1.227–1.800	0.141	1.150 1.012–1.308
		1.487 1.212–1.803		1.160 1.003–1.332
Hematologic dysfunction	0.585	1.798 1.023–3.162	0.287	1.341 1.126–1.598
		1.535 0.987–4.118		1.341 1.139–1.596
Cardiovascular dysfunction	0.313	1.201 1.056–1.674	0.336	1.381 1.235–1.545
		1.361 1.043–1.817		1.383 1.213–1.560
Neurologic dysfunction	0.578	1.787 1.510–2.115	0.636	1.89 1.644–2.242
		1.784 1.549–2.149		1.90 1.640–2.290
Renal dysfunction	0.336	1.40 1.236–1.529	0.182	1.201 1.076–1.340
		1.378 1.227–1.569		1.202 1.082–1.345
	HLstat: 10.3, p = .24, AUC: 0.760		HLstat: 11, p = .17, AUC: 0.784	
Day 7: 294 nonsurvivors/406 survivors (42%)				
Constant	−1.77		−1.71	
Hepatic dysfunction	0.609	1.956 1.189–2.896	0.162	1.188 0.96–1.44
		1.862 1.215–3.283		1.190 0.967–1.420
Pulmonary dysfunction	0.299	1.342 1.093–1.650	0.07	1.13 0.945–1.23
		1.336 1.071–1.686		1.12 0.92–1.36
Hematologic dysfunction	1.14	3.59 1.435–6.520	0.374	1.468 1.21–1.79
		3.191 1.209–9.015		1.510 1.185–1.90
Cardiovascular dysfunction	0.426	1.527 1.201–1.941	0.316	1.37 1.19–1.52
		1.522 1.129–2.090		1.117 1.180–1.504
Neurologic dysfunction	0.507	1.653 1.399–1.954	0.573	1.78 1.53–2.10
		1.681 1.394–2.050		1.80 1.51–2.19
Renal dysfunction	0.265	1.29 1.127–1.402	0.163	1.17 1.05–1.33
		1.266 1.096–1.411		1.182 1.04–1.35
	HLstat: 14, p = .08, AUC: 0.746		HLstat: 6.3, p = .62, AUC: 0.768	

LOD, Logistic Organ Dysfunction; SOFA, Sequential Organ Failure Assessment; OR, odds ratio; CI, confidence interval; HLstat, Hosmer-Lemeshow statistic; AUC, area under the curve-receiver operating characteristics.

Only patients with intensive care unit (ICU) stays of at least n + 1 days were introduced into the analysis. Day n is the nth calendar day in the ICU (day 0 is the calendar day of ICU admission). The respective contributions of each organ dysfunction to each score were tested using logistic regression in the patients with ICU stays of at least n + 1 days. The HLstat measures model calibration. A p value >.05 indicates good calibration. AUC measures overall discrimination by the model.

improvement was more marked with the SOFA score and was significant every day from day 1 to day 7. ROC curves at day 1, 3, and 7 with both scores are in Figure 6.

This improvement in discrimination was probably due to variations in the relative influence of each organ dysfunction in the model. For the LOD system, the relative impact of points obtained for hematologic dysfunction was higher than that of points for other dysfunctions and increased with time. For the SOFA score, points for neurologic and cardiovascular dysfunctions had more impact than points for other dysfunctions (Tables 3 and 4). Each daily organ dysfunction score remained independently associated with mortality (Table 4).

The predictive equation of the original LOD system (14) did not provide a satisfactory fit (Hosmer-Lemeshow chi-square, 364, $p < 10^{-4}$). The original model underestimated the observed hospital mortality at each LOD score level. After customization, both the LOD and the SOFA showed satisfactory calibration with model 1 (Table 2) and model 2 (Table 4). Observed vs. expected hospital mortality for day 1, 3, and 7 model are in Figure 7.

Seven hundred patients were hospitalized for >8 days. Daily LOD scores from day 1 to day 7 were very significantly higher in nonsurvivors (Fig. 8). The total score remained higher in nonsurvivors but decreased in survivors. LOD and

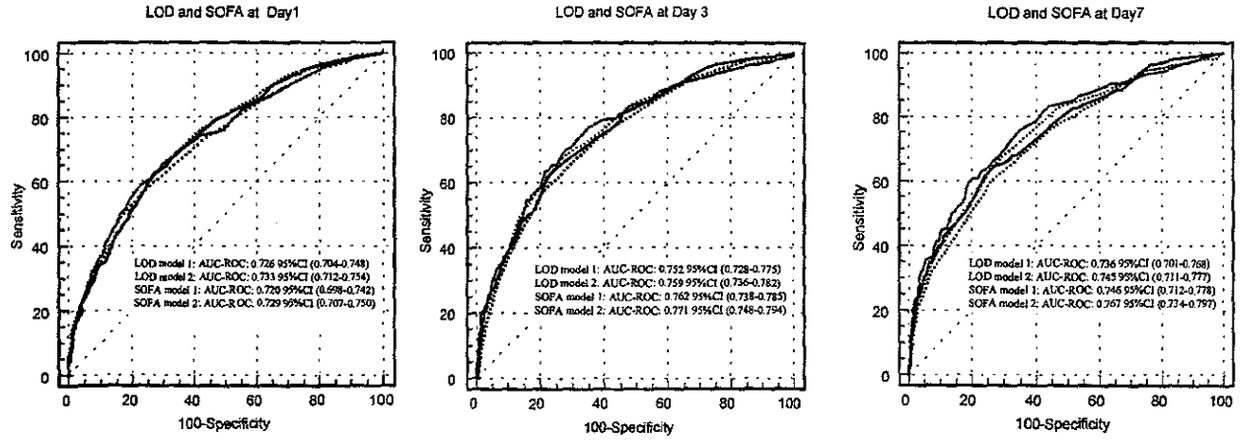

Figure 6. Receiver operating characteristics (*ROC*) curves of the customized daily Logistic Organ Dysfunction (*LOD*) and Sequential Organ Failure Assessment (*SOFA*) scores. *AUC*, area under the curve: *black dotted line*, LOD model 1: *black line*, LOD model 2; *gray dotted line*, SOFA model 1: *gray line*, SOFA model 2. See the text for the definitions of models 1 and 2.

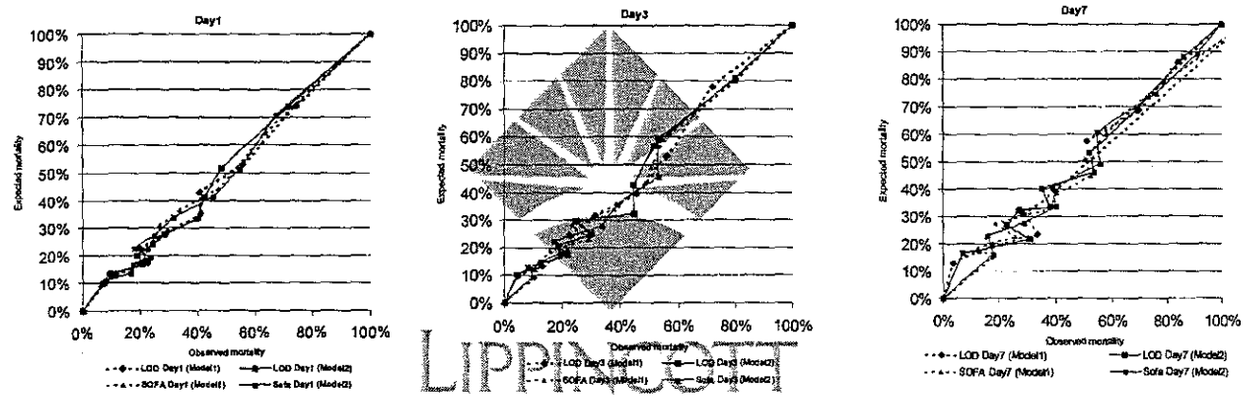

Figure 7. Observed vs. expected hospital mortality according to customized Sequential Organ Failure Assessment (*SOFA*) and Logistic Organ Dysfunction (*LOD*) scores. See the text for the definitions of models 1 and 2.

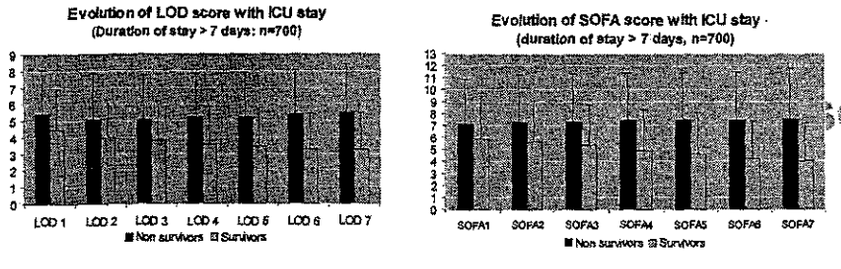

Figure 8. Changes in Sequential Organ Failure Assessment (*SOFA*) and Logistic Organ Dysfunction (*LOD*) scores in patients with intensive care unit (*ICU*) stays of ≥8 days. All differences between survivors and nonsurvivors were highly significant ($p < 10^{-4}$). *Grey bars*, survivors (n = 406); *black bars*, nonsurvivors (n = 294). Data presented as mean ± SD.

SOFA scores were highest on day 2 (25th percentile, day 0; 75th percentile, day 4). Finally, the SOFA score decreased more in survivors than in nonsurvivors from day 1 to day 7 (65% vs. 42%, respectively, $p < 10^{-4}$). Similarly, the LOD score decreased more in survivors than in nonsurvivors (62% vs. 42%, respectively, $p < 10^{-4}$) during the same period.

DISCUSSION

In this study, we assessed the accuracy of daily LOD and SOFA scores in predicting hospital mortality of critically ill patients. We also compared the characterization of multiple organ dysfunction by the SOFA and LOD scores. These scores were designed using very different methods: The LOD system was derived from a multiple logistic regression model (14), whereas the SOFA system was developed during a consensus conference (15) and tested in a prospective multicenter study (13). Moreover, the SOFA score was specifically designed to better describe multiple organ failure (or morbidity), and it includes several therapeutic variables (such as inotropic support). It has been found useful in cardiac (20) and trauma patients (21). On the contrary, the LOD score was designed as a tool for evaluating the probability of mortality based on organ dysfunction on the day of ICU admission, not for measuring the severity of each organ dysfunction day after day.

Both the daily Logistic Organ Dysfunction score and the daily Sequential Organ Failure Assessment score accurately predict intensive care unit mortality at any time during the first intensive care unit week and should be used to estimate the contribution of severity of the underlying illness to the risk of death.

Nevertheless, a recent article by Metnitz et al. (22) suggested that the LOD score was effective in quantitating the severity of each organ failure on the first ICU day.

In our large database study, we found that both the LOD and the SOFA scores characterized the progression of multiple organ dysfunction during the first ICU week. Both scores showed good internal consistency; for each of the six organ dysfunctions, mortality increased from one level of severity to the next (Table 3). Moreover, after first-level customization, both scores were reasonably accurate in predicting hospital mortality. First-level customization models (which are based on the total organ dysfunction score) are extremely easy to compute. The first-level customized versions of the two scores used in our study showed similar discrimination for predicting mortality during the first ICU week.

As previously reported, aggregate scores may be misleading because it cannot be established that each organ's total score carries the same weight. We found that relative contributions were greatest for hematologic dysfunction with the LOD score and for neurologic dysfunction with the SOFA score. Moreover, the impact of hematologic dysfunction in the LOD system increased from one day to the next. These findings explain why second-level customization, in which each point per organ dysfunction is introduced separately, is more effective in discriminating survivors from nonsurvivors than first-level customization, in which the relative contributions of the organ dysfunctions are pooled.

We performed an internal validation using the bootstrap method that provides an unbiased estimate of covariate effect. It means that our model is still valid if another independent sample of the same population (same case mix, severity, and mortality) is selected. However, it remains to be validated in another ICU population. In other institutions where the case mix is different, calibration should be used. Both first and second level calibration could be used. The second one should improve the discrimination of the score.

Although tools predicting outcomes for a group of patients are useful for planning and evaluating care and for obtaining comparable patient populations in clinical trials, these same tools may lack accuracy for describing the course of these patients in the ICU. Survival of critically ill patients does not depend on the occurrence of a single event; changes in existing organ dysfunctions and development of new organ dysfunctions play a role also. To describe organ dysfunction as a clinical outcome, scores such as the Multiple Organ Dysfunction Scale (23), Organ Dysfunction and/or Infection (24), LOD, and SOFA have been developed. Daily organ dysfunction scores, once validated and correctly calibrated, may considerably improve our ability to determine how patients are faring in the ICU. They could be used to monitor the clinical course of an individual patient, to describe the acuity of an illness at a given time point (and, by inference, to make optimal decisions regarding the number of nurses needed), and to identify targets for quality improvement efforts. Further application of the model to a different population can only be done once the system has been tested and validated on that population. Only subsequently can the equation be used to examine outcome difference and to identify areas of potential improvement of the quality of care. The accuracy of these scores, even recalibrated, remains too low to allow reliable individual mortality prediction (Appendixes 1 and 2).

Daily organ score could also be used to determine the baseline severity of illness for patients enrolled in clinical trials and to quantify their response to therapy (25) and thus could serve as a basis for evaluation of specific therapeutic interventions. The ICU mortality should have been used alternately as the end point of interest. The assessment of ICU mortality is readily available without any additional effort. The discrimination of both scores were slightly higher when using it (data not shown). However, hospital mortality is thought to be a more reasonable approach because it is not skewed by different ICU discharge practices, which may vary across regions and countries and give erroneous mortality figures. For example, the post-ICU mortality ranged between 0% and 63.2% in 23 Austrian ICUs (22). This variability supports the use of hospital mortality.

During the first ICU week, severity on the current day is the most important predictor of hospital mortality. For example, in a study by Wagner et al. (12), the acute physiology score on the current day contributed 54% of hospital mortality prediction as compared with only 5% for the acute physiology score at admission. Using the multi-processing model (MPM) (11) or the Acute Physiology and Chronic Health Evaluation (APACHE) III (12), prediction of the probability of mortality obtained from the score calculated on the current day was not significantly improved by those obtained from the previous day (11). Discrimination using daily customized MPM II scores ranged from 0.787 to 0.823 and was better than prediction in our study with the LOD and SOFA (11). However, in our study, patients who died or who were discharged alive on the current day were not entered in the multivariate analysis, and this artificially decreased discrimination by both scores.

In studies of long-stay ICU patients, severity scores at admission failed to predict mortality. In a study by Ferraris et al. of 110 patients with ICU stays of ≥72 hrs, occurrence in the ICU of nosocomial sepsis, iatrogenic events, and renal failure was associated with ICU mortality, whereas APACHE II at admission was not.

Similarly, neither the mean APACHE II score (3) nor the mean MPM II score (4) at admission differed between patients with fatal or clinically resolved nosocomial pneumonia. In ICU-acquired septic shock, the APACHE II, Multiple Organ Dysfunction Scale, and Organ System Failure scores failed to discriminate between survivors and nonsurvivors (5).

A few data in the literature suggest that severity scores calculated throughout the ICU stay may be more accurate in predicting death of patients with nosoco-

mial infection. Girou et al. (10) studied 42 ICU patients with nosocomial infections and 42 controls matched on baseline severity of illness (as assessed by the APACHE II score at admission and age) and duration of risk exposure. Although baseline severity of illness was identical in the cases and controls, mortality was 58.5% in the cases as compared with 14.6% in the controls ($p < .001$). Whereas severity scores at admission failed to predict mortality, the APACHE II score and the Simplified Acute Physiology Score in the cases on the third ICU day, before the occurrence of nosocomial infection, were significantly higher than those in the controls. Similarly, we previously reported that the LOD score measured 3 or 7 days before the diagnosis of catheter-related bacteremia was associated with mortality in ICU patients independently from severity at admission (8). Finally, both the daily LOD score and the daily SOFA score accurately predict ICU mortality at any time during the first ICU week and should be used to estimate the contribution of severity of the underlying illness to the risk of death.

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APPENDIX 1. Logistic Organ Dysfunction Score (14)

	5	3	1	0	1	3	5
Neurologic							
Glasgow Coma Score	3–5	6–8	9–13	14–15	—	—	—
Cardiologic							
FC, beats/min	<30	—	—	30–139	≥140	—	—
	or			and	or		
SBP, mm Hg	<40	40–69	70–89	90–239	240–269	≥270	—
Renal							
Urea nitrogen, mmol/L (g/L)	—	—	—	<6 (<0.36)	6–9.9 (0.36–0.59)	10–19.9 (0.60–1.19)	≥20 (≥1.20)
				and	or	or	
Creatin, μmol/L (mg/dL)	—	—	—	<106 (<1.20)	106–140 (1.20–1.59)	≥141 (≥1.60)	—
				and		or	
Urine output, L	<0.5	0.5–0.74	—	0.75–9.99	—	≥10	
Pulmonary							
Pao_2 (mm Hg)/Fio_2 on MV_{ou} CPAP		<150	≥150	No MV	—	—	—
or				No CPAP			
Pao_2 (kPa)/Fio_2		<19.9	≥19.9	No IPAP	—	—	—
Hematologic							
Leukocytes, $\times 10^9$/L	—	<1.0	1.0–2.4	2.5–49.9	≥50.0	—	—
			or	and			
Platelets, $\times 10^9$/L	—	—	<50	≥50			
Hepatologic							
Bilirubin, μmol/L (mg/dL)	—	—	—	<34.2 (<2.0)	≥34.2 (≥2.0)	—	—
				and	or		
Prothombin time secs above standard (%)	—	—	(<25)	≤3 (≥25)	>3	—	—

FC, functional capacity; SBP, systolic blood pressure; MV, mechanical ventilation; CPAP, continuous positive airway pressure; IPAP, inspiratory positive airway pressure.

APPENDIX 2. Sequential Organ Failure Assessment score (15)

	0	1	2	3	4
Pulmonary					
Pao_2/Fio_2, mm Hg	>400	≤400	≤300	≤200 and mechanical ventilation	≤100 and mechanical ventilation
Hematologic					
Platelets (giga/L)	>150	≤150	≤100	≤50	≤20
Hepatologic					
Bilirubin, mg/dL	<1.2	1.2–1.9	2–5.9	6–11.9	>12
μmol/L	<20	20–32	33–101	102–204	>204
Cardiovascular		Mean blood pressure <70 mm Hg[a]	Dopamine ≤5 gamma or Dobutamine[a]	Dopamine ≥5 or Epinephrine ≤0.1 or Norepinephrine ≤0.1 Gamma/kg/mn[a]	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1 Gamma/kg/mn[a]
Neurologic					
Glasgow	15	13–14	10–12	6–9	<6
Renal					
Creatin, μmol/L	<110	110–170	171–299	300–440 or <500 mL/day	>440 or <200 mL/day
Urine output					

[a] Norepinephrine, epinephrine, dopamine, and dobutamine administered for at least 1 hr.

ANNEXE 3

The Significance of Distal Bronchial Samples With Commensals in Ventilator-Associated Pneumonia*

Colonizer or Pathogen?

Olivier Lambotte, MD; Jean-François Timsit, MD; Maïté Garrouste-Orgeas, MD; Benoit Misset, MD; Adel Benali, MD; and Jean Carlet, MD

Study objective: **To investigate the role of oropharyngeal and cutaneous commensal microorganisms (OCCs) as a cause of ventilator-associated pneumonia (VAP).**
Design: **Retrospective analysis of the medical and microbiological records.**
Setting: **One medical-surgical ICU.**
Patients: **All VAP episodes recorded during a 10-year period were reviewed. All patients with suspected VAP underwent bronchoscopy with protected-specimen brush (PSB) sampling and BAL before any change in antibiotic therapy was made. OCC-VAP was defined as VAP with significant growth in quantitative cultures (PSB yielded $\geq 10^3$ cfu/mL and/or BAL yielded $\geq 10^4$ cfu/mL) of OCCs only. Three experts reviewed the episodes. Exposed patients (*ie*, those with OCC-VAP) and unexposed patients (*ie*, patients without VAP) matched on condition severity at ICU admission and mechanical ventilation duration were compared.**
Results: **Twenty-nine episodes in 28 patients with $\geq 10^4$ cfu/mL OCCs in BAL fluid and/or $\geq 10^3$ cfu/mL OCCs in PSB specimens were found. All patients in these episodes had new radiologic lung infiltrates, with 26 episodes involving purulent tracheal aspirates, 23 episodes involving temperatures $\geq 38.5°C$, and 18 episodes involving $\geq 11{,}000$ leukocytes/μL. The main OCCs found were non-β-hemolytic Streptococcus spp (n = 12), Neisseria spp (n = 7), and coagulase-negative Staphylococcus spp (n = 6). Other possible reasons for fever and the presence of new chest infiltrates were found in 20 and 17 patients, respectively. Histologic evidence of pneumonia was found in 2 of the 10 patients who died. The three experts agreed on the diagnosis for 23 patients. In the OCC-VAP group only, the mean (± SD) logistic organ dysfunction (LOD) scores increased significantly (LOD score, 2 ± 4; p = 0.008) during the 3 days before bronchoscopy, and ICU stay duration was longer than in the unexposed group. The exposed/unexposed study found no difference in mortality.**
Conclusion: **OCCs may behave like classic nosocomial pathogens in critically ill patients.**
(CHEST 2002; 122:1389–1399)

Key words: BAL; coagulase-negative staphylococci; Neisseria spp; nosocomial infection; protected-specimen brush; *Streptococcus epidermidis*; Streptococcus spp; ventilator-associated pneumonia

Abbreviations: CGNS = coagulase-negative Staphylococcus; CI = confidence interval; CPIS = clinical pulmonary infection score; ICO = intracellular organism; IMV = invasive mechanical ventilation; LOD = logistic organ dysfunction score; MIC = minimum inhibitory concentration; OCC = oropharyngeal or cutaneous commensal microorganism; OR = odds ratio; PSB = protected-specimen brush; SAPS = simplified acute physiology score; VAP = ventilator-associated pneumonia

The diagnosis of ventilator-associated pneumonia (VAP) is often difficult because many other conditions can produce sepsis and new lung infiltrates in critically ill patients.[1,2] Significant numbers of a nosocomial pathogen in quantitative cultures of bronchial specimens convert a suspicion of VAP to a near certainty. A protected-specimen brush (PSB) culture showing at least 10^3 cfu/mL, a positive result of a BAL fluid smear, or a BAL fluid culture with at least 10^4 cfu/mL is specific for VAP in patients without recent changes in antimicrobial therapy.[2,3]

The organisms most often responsible for VAP are methicillin-resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and Enterobacteriaceae. In early-onset VAP, *Streptococ-*

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cus pneumoniae, Haemophilus influenzae, and methicillin-sensitive *S aureus* are causative pathogens.

Significant growth of oropharyngeal or cutaneous commensal microorganisms (OCCs) in quantitative cultures of distal bronchial specimens are more difficult to interpret. Because their virulence is low, OCCs are widely believed to be nonpathogenic.[4] The presence in distal bronchial specimens of microorganisms such as Neisseria spp, Corynebacterium spp, or coagulase-negative Staphylococcus (CGNS) is often considered to indicate lung colonization or specimen contamination.

However, there is ample evidence that these same species can produce various infections in both immunocompetent and immunocompromised hosts.[5–10] Numerous studies[11,12] have shown that critically ill patients have complex deficiencies in both cellular and humoral immunity. Moreover, OCCs have been found in lung cultures in postmortem studies.[13,14] These data may prompt ICU physicians to treat patients with OCCs in distal bronchial specimens.

Most studies investigating the potential role of OCCs as lung pathogens[15–21] have reported the rate of OCC recovery in series of patients with VAP. The meaning of significant growth in quantitative cultures of OCCs has been neither investigated in depth nor discussed in reviews or consensus conferences about VAP.[22,23]

To evaluate the meaning of OCC-positive quantitative distal bronchial cultures in patients with suspected VAP, we retrospectively reviewed the records of patients with VAP included in the database of our ICU. We identified those patients in whom only one or more OCCs were found in significant concentrations in distal bronchial cultures (OCC-VAP). We evaluated the degree of confidence with which experts diagnosed VAP caused by OCCs in these patients, and we conducted an exposed/unexposed study to look for organ dysfunction and/or excess mortality associated with OCC-VAP.

Materials and Methods

Study Population

For the last 10 years, all patients with nosocomial infections seen in our ICU have been prospectively recorded in a computer database. Our 10-bed polyvalent ICU is in a 465-bed teaching hospital that serves both as a referral center and as a primary care center. VAP prophylaxis was carried out in compliance with the guidelines of the Comité Technique des Infections Nosocomiales.[24] In particular, endotracheal suctioning was performed at 3-h intervals at a pressure of < -80 cm H_2O using a sterile disposable catheter that was handled with sterile compresses and nonsterile gloves by nurses who washed their hands before and after the procedure.

We reviewed all VAP episodes recorded between August 1, 1990, and August 1, 2000, and selected the records of patients with significant growth in quantitative cultures of distal bronchial specimens of OCCs only. We excluded patients with AIDS, neutropenia (*ie*, < 500 neutrophils/μL), hematologic malignancies, or a change in antimicrobial therapy within 3 days before the bronchoscopy that provided the diagnosis of VAP. For each case of VAP, we recorded body temperature, peripheral leukocyte count, the presence of a purulent tracheal aspirate, and the presence of a new chest radiograph infiltrate within 48 h before the bronchoscopy. A clinical pulmonary infection score (CPIS) was calculated for each patient.[25]

Definitions and Diagnosis of OC-VAP

VAP was defined as any lower respiratory tract infection that developed ≥ 48 h after ICU admission in patients receiving invasive mechanical ventilation (IMV). A clinical suspicion of pneumonia was defined as the presence of a new or persistent lung density seen on chest radiographs with one or more of the following conditions: temperature of > 38.5°C or < 36.5°C; peripheral leukocyte count of $> 11{,}000$ cells/μL or $< 5{,}000$ cells/μL; and the presence of purulent endotracheal aspirate. All patients with clinically suspected pneumonia underwent fiberoptic bronchoscopy with PSB sampling and BAL before any change in antibiotic therapy was made. Specimens were collected and processed as described elsewhere.[26] The study team was very familiar with these techniques, which have not been changed in the last 10 years. VAP was diagnosed if the PSB specimen yielded $\geq 10^3$ cfu/mL and/or the BAL fluid yielded $\geq 10^4$ cfu/mL. Legionella pneumonia was diagnosed based on a positive result of a qualitative culture, urinary antigen test, or serum antibody test for the organism. Chlamydia spp and Mycoplasma spp were tested for in a few patients, none of whom had positive results.

OCC-VAP was defined as the presence of VAP with significant growth in quantitative cultures of OCCs only. The organisms were as follows: Streptococcus spp other than β-hemolytic streptococci (groups A, C, and G, and *S pneumoniae*); Neisseria spp: *Moraxella catarrhalis*; Corynebacterium spp; Haemophilus spp other than *H influenzae*; and CGNS other than *Staphylococcus lugdunensis*. Cases of VAP with the growth of one or more OCCs and at least one organism known to be pathogenic were excluded.

Differential Diagnosis

Patients with suspected VAP were routinely screened for other causes of lung density and fever. The definitions of these causes were adapted from Meduri et al[1] and are listed below.

1. Atelectasis: resolution of pulmonary densities within 48 h of bronchoscopy without antibiotic therapy;
2. Congestive heart failure: hemodynamic evidence of increased pulmonary artery occlusion pressure or resolution of pulmonary densities within 48 h after bronchoscopy and after diuretic therapy initiation;
3. Deep venous thrombosis: positive Doppler ultrasound findings in the lower limb veins followed by treatment with anticoagulant agents;
4. Pulmonary embolism: suggestive findings on a ventilation-perfusion scintigram or angio-CT lung scan followed by anticoagulant therapy;
5. Drug fever: resolution of fever with drug withdrawal and recurrence of fever with the administration of a drug of the same class;
6. Surgical site infection: discharge of pus from a surgical wound.

7. Catheter-related infection: $\geq 10^3$ cfu/mL in semiquantitative cultures of the catheter tip with at least one blood culture yielding the same microorganism and/or at least partial sepsis improvement after catheter removal;
8. Peritonitis: positive findings of cultures of a peritoneal fluid aspirate;
9. Sinusitis: definitive diagnosis consists of both a CT scan showing a sinus air-fluid level or density and a positive maxillary aspirate culture; presumptive diagnosis consists of a CT scan showing an air-fluid level or density in all the sinuses and no sinus aspirate available;
10. Urinary tract infection: urinary culture yielding 10^5 cfu/mL;
11. Intra-abdominal infection: intra-abdominal abscess or any abdominal ultrasound and/or CT scan findings that led to surgery; and
12. ARDS: new bilateral pulmonary infiltrates on the chest radiograph, PaO_2/fraction of inspired oxygen ratio of ≤ 200 mm Hg, and a requirement for mechanical ventilation, without heart failure.

In all patients, blood and urine cultures were performed within 3 days before undergoing the bronchoscopy. Central venous lines were routinely changed in patients with local inflammation, prolonged unexplained fever, and/or positive blood cultures. A sinus CT scan was performed only if there was a purulent posterior nasal drip. Abdominal CT scans, ultrasound scans, venous Doppler ultrasound studies, and investigations for pulmonary embolism were performed as indicated.

Medical Record Review by Senior Physicians

Each case was independently and blindly reviewed by three senior physicians with extensive experience in the management of VAP. Each of these experts was asked to answer the following five questions: (1) Do you believe the prebronchoscopy findings indicate a suspicion of VAP? (1a) How confident are you that your previous answer is correct (on a four-item verbal scale, from limited confidence to complete confidence)? (2) Do you believe that the findings, including the microbiological results, indicate a diagnosis of VAP? (2a) How confident are you that your previous answer is correct (same scale as in question 1a)? and (3) Would you have given antibiotics selected for activity against one or more OCCs? To agree or to reject the possible VAP diagnosis, experts used arguments adapted from a previous report from our team,[26] which were based on the recovery of the patient with or without effective antimicrobial therapy and on a proven or suspected alternate diagnosis.

Data Analysis

To find out whether OCC-VAP was associated with increased illness severity, we determined the logistic organ dysfunction (LOD) score[27] at ICU admission, 3 days before undergoing the bronchscopy (D3), and on the day of the bronchoscopy (D0). We estimated the risk of mortality related to OCC-VAP in an exposed/unexposed analysis. Unexposed patients were defined as patients in whom VAP had neither been diagnosed nor suspected.

Assuming a 35% mortality rate in non-VAP patients (*ie*, patients receiving IMV but free of VAP), and given that only 28 patients had OCC-VAP, two no-VAP patients per OCC-VAP patient were needed to detect a twofold mortality increase in OCC-VAP patients, with a power of 80% and a type I error rate of 5%. A list of no-VAP patients was retrieved from the database. Each OCC-VAP patient was matched with two no-VAP patients on the following characteristics: calendar period of ICU hospitalization; IMV duration (required, in no-VAP patients, to be at least equal to that in the corresponding OCC-VAP patient before the day they underwent the bronchoscopy); predicted mortality as assessed by simplified acute physiology score (SAPS) II score at ICU admission (± 10%); and sex. Appropriate no-VAP patients were identified by reviewing the database records of all patients admitted to the ICU during the study period, except for those with OCC-VAP. A software macro (SAS; SAS Institute; Cary, NC) was used to select no-VAP patients without input from the investigators. The medical records of no-VAP patients were reviewed to calculate the LOD score at ICU admission, LOD score after the ICU stay duration at which the matched OCC-VAP patient underwent bronchoscopy (LOD-D0; *ie*, when the IMV duration was equal to that in the matched OCC-VAP patient), and 3 days before D0 (*ie*, LOD-D3).

Statistical Analysis

Patient characteristics are presented as the mean ± SD or No. (percentages). Two-way analysis of variance on ranks were used for continuous data and a two-covariates logistic model for qualitative data (in both cases, one factor was exposure and the other was the triplet formed by each OCC-VAP patient and the two matched no-VAP patients). Survival in OCC-VAP and no-VAP patients was compared using conditional logistic regression. A Wilcoxon test for paired data was done to compare LOD scores before and at the time of OCC-VAP. All statistical tests were run by a statistical software package (SAS, version 6.12; SAS Institute). All tests were two-sided, and p values ≤ 0.05 were considered to be statistically significant.

Results

VAP Patients

Three thousand five hundred fifty-four patients were admitted to our ICU during the 10-year study period. Of these, 1,955 patients (55%) received IMV, and 292 patients had 369 episodes of VAP. There were 77 episodes of polymicrobial pneumonia with the significant growth of one or more classic nosocomial pathogens and one or more OCCs. These cases were not included in the OCC-VAP category. Thirty-three episodes of OCC-VAP occurred in 32 patients, accounting for 9% of all VAP cases (33 of 369 cases). The overall rate of occurrence of OCC-VAP was 0.9 per 1,000 patients admitted to the ICU. Four OCC-VAP episodes in four patients were excluded because of incomplete data (n = 2) or because the patients had AIDS (n = 2). This left 29 OCC-VAP episodes in 28 patients (16 men and 12 women) who had a mean age of 68 ± 10 years (age range, 34 to 82 years). Twenty-five patients had chronic conditions including the following: heart failure (6 patients); COPD (five patients, including one receiving long-term oral glucocorticoid therapy of < 0.5 mg/kg/d); vasculitis (caused by rheumatoid arthritis in two patients, Wegener granulomatosis in one patient, and giant cell arteritis in one patient) requiring glucocorticoid therapy of > 0.5 mg/kg/d and/or immunosuppressive therapy (*ie*, cyclophos-

phamide or methotrexate); diabetes mellitus (four patients) or a solid malignancy treated without chemotherapy (six patients).

All 28 patients received IMV for a mean duration of 23 ± 20 days. Ten cases of OCC-VAP occurred before the sixth ICU day, and 19 cases occurred beyond the sixth ICU day. Of the 29 episodes of OCC-VAP, 10 occurred within the first 5 days of the patient receiving IMV.

All 29 OCC-VAP episodes were characterized by a new chest infiltrate, 26 by a purulent tracheal aspirate, 23 by a fever of 38.5°C, and 18 by a leukocyte count of > 11,000 cells/μL. Two, three, or four of these symptoms were present in 29, 17, and 8 episodes, respectively. The mean CPIS was 7.6 ± 1.95, and the median CPIS was 8. The CPIS was > 6 in 20 cases. Bacteriologic data are shown in Table 1. Both PSB sampling and BAL were performed in 22 episodes. In eight episodes, both the PSB and the BAL fluid cultures were positive and the BAL fluid smear showed > 5% intracellular organisms (ICOs); in five episodes, both cultures were positive but the BAL fluid smear showed < 5% ICOs; in four episodes, either the PSB specimen or the BAL fluid culture was positive with > 5% ICOs; and in 12 episodes, either the PSB or the BAL fluid culture was positive and < 5% ICOs were observed. In two patients, an autopsy performed within 3 days after the bronchoscopy showed histologic evidence of pneumonia. In the patient in whom the lung was cultured, no OCCs were recovered, but effective antibiotic therapy was given between the time that the patient underwent bronchoscopy and death. In two other patients who had OCC-VAP with the presence of CGNS, a CT scan showed lung abscesses.

Forty-seven OCCs were recovered during the 29 episodes of OCC-VAP, 34 in concentrations above the cutoffs defining positive quantitative cultures (Table 2). In 10 episodes, more than one OCC was recovered, and 9 of these 10 episodes occurred within 8 days after intubation. The mean bacterial index[25] was 5.8 (median, 5; SD, 2.7) for the 29 episodes and 8.3 ± 2.8 for the 10 polymicrobial episodes.

In six episodes with CGNS, no other organisms were found. *Streptococcus epidermidis* was involved in five cases. The numbers of patients with two, three, or four criteria for a clinical suspicion of VAP were two, three, and one, respectively. One of these six episodes occurred in a patient receiving glucocorticoid therapy, > 1 mg/kg, and methotrexate therapy for rheumatoid arthritis. Five episodes occurred > 5 days after intubation. Only in two episodes did the BAL fluid smear show > 2% ICOs, and although all PSB cultures were positive, only two episodes had BAL fluid cultures with > 10^4 cfu/mL. In three episodes, community-acquired pneumonia had been the reason for ICU admission and was a possible cause for the lung infiltrate, heart failure was present in two other episodes, whereas in the remaining episode there was no alternative diagnosis. Lung abscesses were demonstrated by CT scans in two patients who had VAP with *S epidermidis*. Three of these six patients received antibiotics that were active against the recovered OCCs. One patient died of a cause considered to be unrelated to OCC-VAP.

Nine of the 11 strains of CGNS recovered in the study were resistant to methicillin and fluoroquinolones, and 8 strains were resistant to gentamicin. The minimum inhibitory concentration (MIC) of vancomycin was always < 8 μg/mL. Except for a *Streptococcus oralis* isolate with a high amoxicillin MIC (4 mg/mL) that was responsible for a lack of response to antibiotic therapy, all the Streptococcus strains were sensitive to amoxicillin. All Gram-negative rods were sensitive to third-generation cephalosporins or co-amoxiclav (one strain of *M catarrhalis* and two strains of *Haemophilus parainfluenzae* produced a β-lactamase).

The possible causes for disagreement between experts are shown in Table 1. Twenty-three alternative causes of new radiologic infiltrates were found in 17 episodes, and 28 alternative causes of fever were found in 20 episodes. In 11 episodes, there was an alternative explanation to both the fever and the new radiologic infiltrate. Only in four episodes was there no alternative diagnosis for the fever or new radiologic infiltrate.

The physicians in charge of the patients decided to treat 22 episodes, although the antimicrobial agents used were active against the OCCs in only 20 episodes. Of the seven patients who were not treated for the bronchoscopy findings, two had another infection for which they received antibiotics that were active against the bronchial OCCs. Ten of the 28 patients died. An autopsy was performed in five patients. In two of these five patients, histologic evidence of pneumonia was found. In the three other patients, death occurred later, after the resolution of the VAP.

Therefore, five patients did not receive an antimicrobial agent and two others received inadequate antimicrobial therapy. Among these seven patients, three died and lung abscesses were diagnosed in two. An 80-year-old woman (Table 1, case 4) had a community-acquired pneumococcal pneumonia with shock and acute renal failure; 16 days later, VAP was suspected and methicillin-resistant *S epidermidis* found in PSB specimens and BAL fluid. She re-

Table 1—*Bacteriologic Results and Reasons for Disagreements

Case	PSB	BAL	Intracellular Organisms, %	Experts Agreed on Diagnosis?	Cause of Disagreement
1	10^3 Neisseria	1.5×10^4 Neisseria	20	VAP by OCCs	
2	10^4 *S oralis*	10^5 *S oralis*, 6 10^2 *Streptococcus mitis*	1	Disagreed	Alternate Dg (DVT)
3	10^5 α-streptococci, 10^3 Neisseria, 10^2 CGNS	7×10^3 α-streptococci, 10^3 Neisseria, 2×10^3 CGNS, 10^3 Corynebacterium	10	No VAP by OCCs	Atelectasis
4†	6×10^3 *S epidermidis*	3×10^3 *S epidermidis*	3	Disagreed	Abcess possibly due to CAP
5	2×10^3 *S oralis*, 2×10^3 *Streptococcus salivarius*	2×10^3 *S oralis*, 2×10^3 *S salivarius*	0	No VAP by OCCs	Recovery without AB
6‡	10^4 *Corynebacterium striatum*, 2.5×10^2 CGNS, 5×10^2 α-streptococci, 2.5×10^2 *H parainfluenza*	10^4 *C striatum*, 2.5×10^2 CGNS, 5×10^{22} α-streptococci, 2.5×10^2 *H parainfluenza*	26	Disagreed	CHF (PCWP > 18 mm Hg) explaining symptoms for 1 expert
7	8×10^2 *S salivarius*, 20 *S epidermidis*	10^4 *S salivarius*	0	No VAP by OCCs	Necrotizing pancreatitis
8	ND	10^4 α-streptococci, 2.6×10^3 *Staphylococcus hominis* 10^3 *N mucosa*, 8×10^2 *H parainfluenza*	25	VAP by OCCs	
9	0	10^4 *N elongata*	0	No VAP by OCCs	Recovery without AB
10	7×10^3 *S epidermidis*	10^3 *S epidermidis*	0	No VAP by OCCs	Unresolved CAP
11	5.5×10^3 *S epidermidis*	ND		No VAP by OCCs	CAP and atelectasis recovery without AB
12	10^5 *H parainfluenza*, 10^5 *Neisseria subflava*	10^5 *H parainfluenza*, > 10^5 *N subflava*	100	VAP by OCCs	
13	5×10^3 *S epidermidis*	2.8×10^3 *S epidermidis*	0	No VAP by OCCs	Recovery without AB, CHF, UTI, and DVT, explaining symptoms
14	10^7 *H parainfluenza*	10^7 *H parainfluenza*	40	VAP by OCCs	
15	7.2×10^3 *M catarrhalis*	ND		VAP by OCCs	
16	10^5 *H parainfluenza*	ND		VAP by OCCs	
17	3×10^4 *S oralis*	3×10^4 *S oralis*	10	VAP by OCCs	
18	10^5 *H parainfluenza*	10^5 *H parainfluenza*	80	VAP by OCCs	
19	ND	1.15×10^4 α-streptococci	0	No VAP by OCCs	SSI and DVT explaining symptoms for 3 experts
20	2×10^3 *M catarrhalis*	6.5×10^3 *M catarrhalis*	1	Disagreed	MI with ARDS explaining symptoms for 1 expert
21	8×10^3 α-streptococci	8×10^4 α-streptococci	1	Disagreed	CHF explaining symptoms for 2 experts
22†	2×10^3 CGNS	10^4 CGNS	0	No VAP by OCCs	CAP explained abcess recovery without AB
23	2×10^3 *M catarrhalis*	10^7 *M catarrhalis*	0	VAP by OCCs	
24	10^4 *M catarrhalis*	10^5 *M catarrhalis*	10	VAP by OCCs	
25	2.7×10^3 *Neisseria mucosa*, 4×10^3 *Streptococcus mitis* 8×10^2 CNS, 4×10^2 *Neisseria elongata*	ND		VAP by OCCs	
26	0	10^4 *N mucosa*, 2×10^2 α-streptococci	27	VAP by OCCs	
27‡	ND	5×10^4 *S oralis*, 5×10^4 *S sanguis*	28	VAP by OCCs	
28	3.5×10^3 Neisseria	10^5 Neisseria	7	VAP by OCCs	
29	8×10^3 *S epidermidis*	10^5 *S epidermidis*	2	Disagreed	No new radiologic infiltrate for 1 expert

*Dg = diagnosis; DVT = deep venous thrombosis; PE = pulmonary embolism; CAP = community-acquired pneumonia; UTI = urinary tract infection; CHF = congestive heart failure; dis = disease; SSI = surgical site infection; MI = mesenteric infarction; ND = not done; PCWP = pulmonary capillary wedge pressure; AB = antibiotics.

†Lung abscess.

‡VAP diagnosis confirmed by postmortem histology.

ceived a 48-h course of a third-generation cephalosporin, developed a lung abscess 1 week later, and died from multiple organ failure 14 days after the occurrence of OCC-VAP. No autopsy was performed. A 44-year-old man (Table 1, case 17) was admitted to the ICU for meningoencephalitis, had

Table 2—*Microorganisms Recovered in Significant Amounts From Quantitative Distal Cultures in 29 Episodes of OCC-VAP*

Microorganisms	No.
Streptococcus spp	12
Neisseria spp	7
CGNS	6
H parainfluenzae	4
M catarrhalis	4
Corynebacterium striatum	1

S oralis isolated in PSB specimens and BAL fluid 15 days later, and was treated with amoxicillin. Unfortunately, the streptococcal strain had a reduced sensitivity to amoxicillin (MIC, 4 μg/mL) and was still isolated 6 days later in specimens from a PSB procedure and in fluid from BAL, which had been performed because of insufficient or poor improvement. Cefotaxime was prescribed. The patient died 2 months after the ICU admission from multiple organ failure in the setting of Pseudomonas bacteremia. A 70-year-old woman (Table 1, case 27) was admitted to the ICU for acute respiratory failure 1 week after undergoing a pneumonectomy procedure for lung cancer. A bronchoscopy was performed on the day of ICU admission, but no antibiotic therapy was prescribed. A pulmonary embolism was suspected, shock developed, and the patient died the next day. *S oralis* and *Streptococcus sanguis* were isolated from the BAL fluid. An autopsy showed histologic findings of pneumonia without pulmonary emboli. The four other patients survived (Table 1, cases 5, 9, 13, and 22), but three patients had different differential diagnoses (heart failure, two patients; atelectasis, one patient). The last patient, admitted to the ICU for inhalation pneumonia, developed a lung abscess after receiving 10 days of mechanical ventilation. *S epidermidis* was recovered from BAL fluid and PSB specimens. The abscess was drained, but the pus was sterile.

The three experts who reviewed the 29 episodes agreed, before reading the PSB specimen and BAL fluid test results, that VAP was a possibility in 12 episodes but could be ruled out in 4 others. In these 16 episodes, confidence with the diagnosis was almost complete or was complete in 44% and 14% of episodes, respectively. Concerning the PSB and BAL findings, the three experts agreed on 23 episodes (VAP caused by OCCs, 14 episodes; no-VAP caused by OCCs, 9 episodes). Confidence was almost complete and was complete in 44% and 28% of episodes, respectively. The patients in whom the 14 episodes occurred that were considered by all three senior physicians to be VAP caused by OCCs were treated with antibiotics, which were ineffective for the recovered microorganisms in one episode. All three experts agreed that treatment was necessary in 16 episodes and were unnecessary in 7 episodes. The data on the disagreement among are reported in Table 1. The main reason for disagreement among the experts was the relevance of a potential differential diagnosis. A description of patient subsets is provided in Table 3. All three episodes caused by *H parainfluenzae* only and three of four episodes caused by *M catarrhalis* only were categorized by all three physicians as VAP caused by OCCs. In contrast, in none of the episodes with CGNS only did all three physicians agree on a diagnosis of VAP caused by OCCs. The mean number of ICOs in BAL fluid smears was significantly different in episodes for which all three experts gave a diagnosis of VAP caused by OCC than in the other episodes.

OCC-VAP/No-VAP Study

The development of OCC-VAP was associated with a significant increase in disease severity, as assessed by the LOD score (LOD-3D, 3.8 ± 2.5; LOD-D0, 5.9 ± 2.7; p = 0.018). During the corresponding hospitalization days, no significant increase was found in the no-VAP group.

No-VAP patients were matched to OCC-VAP patients by SAPS II score at ICU admission and by IMV duration (which had to be as long or longer as in the OCC-VAP patient) [Table 4]. Matching was always successful for SAPS II score and IMV duration. The crude in-ICU death rate was 36% (10 of 29 patients) among the OCC-VAP patients and 36% (20 of 58 patients) among the no-VAP patients. We found no differences between OCC-VAP and no-VAP patients, except for the LOD score on the day of OCC-VAP (or on the corresponding day in the matched no-VAP patient). OCC-VAP was not associated with excess mortality in the OCC-VAP/no-VAP study (odds ratio [OR], 1.19; 95% confidence interval [CI], 0.41 to 1.72; p = 0.75) even after further adjustment on the LOD score 3 days earlier (OR, 1.19; 95% CI, 0.41 to 3.46; p = 0.8). The mean ICU stay was 6 days longer in the OCC-VAP patients than in the no-VAP patients.

Discussion

We are not aware of earlier studies specifically designed to investigate the role for OCCs in the pathogenesis of VAP. However, OCCs accounted for 9% of VAP episodes that were recorded in our 10-year database and have been found consistently in microbiological series reported in the literature. In series of patients with VAP diagnosed using either a

Table 3—*Comparisons Between the Actual Management of the OCC-VAP Episodes and the Conclusions of Three Experts Who Reviewed the Medical Records Retrospectively

Variables	Treated OCC-VAP Episodes (n = 22)	Untreated OCC-VAP Episodes (n = 7)	Episodes Diagnosed as VAP by OCCs† (n = 14)	Episodes Diagnosed As Not VAP OCCs† (n = 9)	Episodes Requiring AT† (n = 16)	Episodes Not Requiring AT† (n = 7)
Bacterial index	7.6 ± 5.1	5 ± 2.4	6.5 ± 2.5	8.25 ± 7.25	6.15 ± 2.5	9.8 ± 7.8
ICOs in BAL	19.6 ± 28.5	4 ± 10.5	31.5 ± 31.4	0.01 ± 0.03	27 ± 30.8	0.02 ± 0.04
Highest body temperature	39.2 ± 0.7	38.2 ± 1.2	39.2 ± 0.9	38.4 ± 1	39.2 ± 0.8	38.5 ± 1
Highest peripheral leukocyte count	12,886 ± 4,910	13,185 ± 6,405	12,528 ± 4,847	14,544 ± 5,939	11,881 ± 4,876	16,271 ± 5,565
Purulent aspirates/d	13 ± 7.2	8 ± 7	12.7 ± 8.4	9.4 ± 6.7	12.6 ± 8.4	7.6 ± 7.3
Age, yr	68 ± 11	65.3 ± 6.1	66 ± 11	65 ± 7.1	68 ± 12	65 ± 8
SAPS II score	37.4 ± 15.8	39.6 ± 18	35.6 ± 19.5	36.7 ± 10.7	37.25 ± 19.3	32.7 ± 8.4
Polymicrobial VAP	8 (36)	1 (14)	4 (28)	3 (33)	4 (25)	3 (42)
H parainfluenzae VAP	3 (14)	0	3 (21)	0	3 (19)	0
Streptococcal VAP	2 (9)	2 (28)	2 (14)	1 (11)	2 (12.5)	1 (14)
CGNS VAP	4 (18)	2 (28)	0	4 (44)	1 (6)	2 (28)
Neisseria spp VAP	2 (9)	1 (14)	2 (14)	1 (11)	2 (12.5)	1 (14)
M catarrhalis VAP	3 (14)	1 (14)	3 (21)	0	4 (25)	0

*Values given as mean ± SD and No. (%). AT = antimicrobial therapy.
†The three experts agreed about only 23 of the episodes reported in the table.

noninvasive[15–17] or an invasive strategy,[17–21] OCCs contributed 2.6 to 36% of organisms recovered in significant concentrations. Interestingly, studies comparing histologic and microbiological criteria for VAP diagnosis have yielded conflicting data. In two studies,[28,29] significant OCC growth was not found in cultures of biopsies from lungs with histologic pneumonia, whereas in two others[13,14] OCCs contributed 8% and 10%, respectively, of the microorganisms recovered in significant amounts in lung biopsy cultures. OCCs accounted for 0%,[29] 11%,[28] and 60%[13] of the significant cultures of distal samplings in VAP episodes with histologic findings of pneumonia. Moreover, OCCs are chiefly encountered in polymicrobial VAP. Finally, the meaning of significant growth in quantitative cultures of OCCs only remains unclear.

For respiratory infection to occur, at least one of the three following factors must be present: immunodeficiency in the host; an inoculum of microorganisms into the lower respiratory tract that is large enough to overwhelm the host's immune system; or a highly virulent organism. One or more of these three factors were present in our exposed patients.

Many ICU patients have prevalent underlying factors associated with immunodeficiency, such as diabetes mellitus or glucocorticoid therapy. These factors increase the risk of infectious and noninfectious life-threatening events. More importantly, there is ample evidence that critical illness is associated with immune defense impairment. Impairments in neutrophil functions including decreased chemotaxis, poor opsonization, and a limited bactericidal effect have been reported in ICU patients.[30] Anergy is common in critically ill patients.[31,32] A large body of data suggests that, during sepsis, the early inflammatory phase that is driven by inflammatory cytokine production is counterbalanced by a subsequent anti-inflammatory phase (the compensatory anti-inflammatory response syndrome), which can lead to immunodeficiency.[11] Moreover, many studies[12,33,34] have found impairment of local immune defenses in the lungs; endotracheal intubation provides microorganisms with direct access to the distal airways and impairs coughing and mucociliary function. Furthermore, sepsis is associated with decreased neutrophil recruitment and impaired alveolar macrophage function. Finally, cytokine network dysregulation with interleukin-10 production may lead to local immunosuppression.[35] Interestingly, in a study[21] of VAP in trauma patients, a population in which abundant evidence of immunosuppression has been reported, 45% of the microorganisms were OCCs. In addition, therapy with glucocorticoids is being used increasingly in ICUs for the treatment of various conditions,[36] resulting in additional immunosuppression.

Of the OCC-VAP episodes in our study, 76% occurred within 8 days after intubation or extubation, suggesting that the inhalation of oropharyngeal secretions occurring during these procedures or caused during the following days by swallowing dysfunction may increase the risk of OCC-VAP. A study by Valles and coworkers[37] of continuous subglottic secretion aspiration in intubated patients supports this hypothesis. Continuous aspiration was

Table 4—*Subjects Included in the Exposed/Unexposed Study

Variables	OCC-VAP (n = 28)	No VAP (n = 56)	p Value†
SAPS II score	38.3 ± 16	39.2 ± 15.2	0.26
Transfer from hospital ward	21 (75)	37 (66)	0.15
Age, yr	67.6 ± 10	67.8 ± 9	0.93
Gender			
Male	16	42	0.08
Female	12	14	
No surgery	14	26	0.48
Elective surgery	9	13	
Emergency surgery	5	17	
LOD score			
On hospital admission	6.2 ± 3.8	4.8 ± 2.6	0.07
Day 3	3.8 ± 2.5	4.4 ± 1.9	0.57
Day 0	5.93 ± 2.7	4.4 ± 1.9	0.0009
Main diagnosis on hospital (admission)			
Multiple organ failure	2	4	
Shock	8	17	
Acute respiratory failure	10	28	
Coma	2	3	
Other	6	4	
Duration of ICU stay, d	26.9 ± 22	20.3 ± 19	0.024
In-ICU deaths	10 (36)	20 (36)	1

*Values given as mean ± SD or No. (%), unless otherwise indicated.

†Characteristics of patients were compared using two-way analysis of variance on ranks for continuous data and a two-covariates logistic model for qualitative data (in both cases, one factor was exposure and the other was the triplet composed of an OCC-VAP patient and two matched No-VAP patients).

associated with significant reductions in the numbers of Gram-positive cocci and Haemophilus spp and in the incidence of VAP during the first 5 days of IMV, as well as with a significantly greater volume of subglottic secretions aspirated daily in the patients without VAP. The pathophysiology of CGNS-VAP is unclear. Although unlikely, we cannot exclude contamination by organisms on the hands of the nurses who performed aspirations. Hematogenous seeding is another possibility.

Oropharyngeal microorganisms such as viridans streptococci,[9,10] *H parainfluenzae*,[7] Neisseria spp,[5,6] and *M catarrhalis*[38] have been described in patients with community-acquired pneumonia, and *M catarrhalis* has been described in those with nosocomial pneumonia.[39] Viridans streptococci[10,13,14] and, less frequently, *M catarrhalis*[38] have been reported to cause lethal pneumonia. In patients with VAP caused by oropharyngeal microorganisms, viridans streptococci have been recovered from blood,[10] abscess pus,[9] and postmortem lung biopsy specimens[13,14]; *M catarrhalis*[35] has been recovered from blood; and *N mucosa* has been recovered from pleural fluid.[40] Most of these patients were immunodeficient (although those patients with AIDS or hematologic malignancies were not included), but some had normal immune defenses. These clinical data are supported by *in vitro* findings such as the presence of protease production by viridans streptococci.[41]

Our study provides six sources of support for the possibility that OCCs may cause VAP. First, for 14 of the 29 patients, the three experts who independently and blindly reviewed the medical records all gave a diagnosis of OCC-VAP, although the distal bronchial samples showed only one or more OCCs. Second, a microbiological diagnosis of OCC-VAP was associated with a significant increase in LOD scores during the 3 days before the bronchoscopy, whereas no significant change was seen in the matched no-VAP patients during the corresponding hospitalization days ($p = 0.18$ [Wilcoxon test]). Moreover, ICU stay duration was significantly longer in the OCC-VAP group. However, the crude mortality rate was identical among OCC-VAP and no-VAP patients, and, after adjustment for severity scores, no excess mortality was found in the OCC-VAP patients (OR, 1.19; 95% CI, 0.41 to 3.46; $p = 0.8$). The power of the exposed/unexposed study was perhaps too small to detect a small increase in mortality in the OCC-VAP group. Third, the CPIS was > 6 in 20 cases and was 6 in 4 additive cases. Fourth, postmortem histologic findings were consistent with VAP caused by OCCs in two patients, and CT scans of the chest showed lung abscesses in two other episodes. Fifth, the results of both PSB specimen and BAL fluid cultures

were above the cutoffs in 13 episodes. Moreover, the presence of > 5% ICOs in 40% of OCC-VAP patients establishes that these pathogens can mount a significant local inflammatory response. Finally, the outcomes for the seven patients not treated or inefficiently treated are worrying. Three patients died, one with histologic findings that were consistent with VAP and one after the development of a lung abscess.

However, the significant growth of OCCs in distal bronchial samples may reflect the contamination of the samples during collection or the nonpathogenic colonization of the lung. We used standard sampling techniques that are designed to minimize the risk of contamination.[26] In 11 OCC-VAP episodes, there was another condition that could have explained both the fever and the new radiographic infiltrates. However, alternative diagnoses are often present in patients with VAP caused by classic nosocomial pathogens.[1] The percentage of squamous epithelial cells, an indicator of oropharyngeal contamination, was < 1% in all episodes. Another issue is the specificity of positive distal samples for the diagnosis of VAP. In a study[42] of mechanically ventilated patients without signs or symptoms of pulmonary infection and without radiographic infiltrates, the specificities of PSB specimen and BAL fluid cultures were low (59% and 65%, respectively), and the rate of false-positive results was high (41% and 35%, respectively), when 10^3 cfu and 10^4 cfu/mL, respectively, were used as the cutoffs for PSB specimen and BAL fluid cultures. However, the patients received antibiotics before sample collection.[42] In contrast, in a study[43] comparing the PSB procedure and BAL in patients with no recent antibiotic therapy changes, the specificities of the PSB procedure and BAL for the diagnosis of VAP were 89% and 78%, respectively, the standard being histologic and microbiologic lung specimen findings immediately after death. In addition, a recent meta-analysis[3] showed that PSB specimen and BAL fluid cultures are reliable for the diagnosis of VAP, particularly in patients with no recent antimicrobial treatment change. Moreover, in 14 of the episodes, the results of at least two microbiological tests (*eg*, BAL fluid smears, BAL fluid cultures, and/or PSB specimen cultures) were positive. This lends strength to our findings, as specificity has been shown to be better when the results of two or all three tests are positive.[26]

Finally, the degree of confidence with the definite diagnosis between experts was good in only 56% of cases. This was due mainly to the high number of patients with possible or probable alternate diagnoses. Moreover, the confidence in the quantitative bacteriologic results has been probably decreased by the known low pathogenicity of encountered microorganisms

Finally, the main issue is the relevance of our findings to the treatment of patients with suspected OCC-VAP. Unnecessary antibiotic therapy in a patient with lung colonization can induce the emergence of drug-resistant strains, but a failure to treat VAP increases the risk of morbidity[44] and mortality. Oropharyngeal organisms are susceptible to co-amoxiclav or third-generation cephalosporins and, consequently, the American Thoracic Society guidelines for VAP management[22] are valid. CGNS was the only microorganism in five patients with VAP occurring more than 5 days after intubation. In patients with late-onset VAP, the finding of Gram-positive cocci on BAL fluid smears should lead to the administration of vancomycin because it can reflect pneumonia caused by a methicillin-resistant *S aureus*. Consequently, when identification studies show that the Gram-positive organism is a CGNS, the problem is not whether vancomycin should be added to the antibiotic regimen but whether vancomycin should be continued. Because most CGNS strains are resistant to co-amoxiclav, cephalosporins, and methicillin, the recovery of a CGNS sometimes leads to vancomycin prescription. However, few data are available on the pathogenicity of CGNS in the lungs, which remains a matter of debate.[8] Very few well-documented case reports of CGNS pneumonia have been reported: one case of *Staphylococcus saprophyticus* pneumonia in an ICU patient[45]; one case of *Staphylococcus cohnii* community-acquired pneumonia in an AIDS patient[46]; and one case of *S epidermidis* VAP with histologic findings of pneumonia.[13] In our study, there was no alternative diagnosis in one of our CGNS cases, and the two patients with lung abscesses had *S epidermidis* as the only distal bronchial microorganism. Consequently, in a critically ill patient whose status is deteriorating and who has significant amounts of CGNS in distal bronchial quantitative cultures with no firm evidence of another cause, we believe that antibiotics against CGNS should be given.

In conclusion, OCC-VAP accounted for 9% of VAP episodes in our study and was associated with worsening organ dysfunction scores. Although alternative conditions explaining chest abnormalities and fever are common, a new radiographic infiltrate with significant growth in distal bronchial cultures of commensal microorganisms only is highly suggestive of VAP. We suggest that such a condition should be systematically treated except in the case of a stable patient with a strong alternative diagnosis for the lung infiltrate and fever for which the treatment should be discussed case by case. OCCs may have

the same deleterious effects as classic nosocomial pathogens in critically ill patients.

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ANNEXE 4

ATTRIBUTABLE MORBIDITY AND MORTALITY OF CATHETER-RELATED SEPTICEMIA IN CRITICALLY ILL PATIENTS: A MATCHED, RISK-ADJUSTED, COHORT STUDY

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ABSTRACT

OBJECTIVE: To determine the attributable risk of death due to catheter-related septicemia (CRS) in critically ill patients when taking into account severity of illness during the intensive-care unit (ICU) stay but before CRS.

DESIGN: Pairwise-matched (1:2) exposed-unexposed study.

SETTING: 10-bed medical-surgical ICU and an 18-bed medical ICU.

PATIENTS: Patients admitted to either ICU between January 1, 1990, and December 31, 1995, were eligible. Exposed patients were defined as patients with CRS; unexposed controls were selected according to matching variables.

METHODS: Matching variables were diagnosis at ICU admission, length of central catheterization before the infection, McCabe Score, Simplified Acute Physiologic Score (SAPS) II at admission, age, and gender. Severity scores (SAPS II, Organ System Failure Score, Organ Dysfunction and Infection Score, and Logistic Organ Dysfunction System) were calculated four times for each patient: the day of ICU admission, the day of CRS onset, and 3 and 7 days before CRS. Matching was successful for 38 exposed patients. Statistical analysis was based on nonparametric tests for epidemiological data and on Cox's models for the exposed-unexposed study, with adjustment on matching variables and prognostic factors of mortality.

RESULTS: CRS complicated 1.17 per 100 ICU admissions during the study period. Twenty (53%) of the CRS cases were associated with septic shock. CRS was associated with a 28% increase in SAPS II. Crude ICU mortality rates from exposed and unexposed patients were 50% and 21%, respectively. CRS remained associated with mortality even when adjusted on other prognostic factors at ICU admission (relative risk [RR], 2.01; 95% confidence interval [CI_{95}], 1.08-3.73; $P=.03$). However, after adjustment on severity scores calculated between ICU admission and 1 week before CRS, the increased mortality was no longer significant (RR, 1.41; CI_{95}, 0.76-2.61; $P=.27$).

CONCLUSION: CRS is associated with subsequent morbidity and mortality in the ICU, even when adjusted on severity factors at ICU admission. However, after adjustment on severity factors during the ICU stay and before the event, there was only a trend toward CRS-attributable mortality. The evolution of patient severity should be taken into account when evaluating excess mortality induced by nosocomial events in ICU patients (*Infect Control Hosp Epidemiol* 1999;20:396-401).

Catheter-related septicemia (CRS) represents the most frequently life-threatening complication of central vascular catheter use.[1,2]

Several studies have reported that, in the intensive-care unit (ICU), bloodstream infections are associated with an increase in morbidity, mortality (10%-40%), length of hospital stay, and finally in medical costs.[3-6] However, the consequences induced by catheter-related bloodstream infections on morbidity and mortality have not been clearly evaluated and remain under debate. Most studies[1,7-9] have suggested that CRS is associated with a lower attributable mortality than other septicemias, but some have found CRS to be associated with marked morbidity.[10,11]

These controversial results are explained in part by the difficulties in estimating the mortality attributable to CRS. Notably, patients' comorbidities, either preexistent or occurring during the ICU stay, have never been taken into account as potential confounding factors in estimating the possible excess of mortality due to CRS. One might anticipate that a patient remaining very sick (for whatever reason) will have a higher risk to develop a nosocomial infection than a patient severely sick at admission but improving quickly. Thus, we assessed the impact of CRS on ICU mortality, paying particular attention to confounding factors.

First, a case study was performed to describe patients with ICU-acquired CRS, focusing on the morbidity of this infection. Then, a matched exposed-unexposed retrospective cohort study was conducted, with three main purposes: (1) to examine the risk of death in patients who developed central CRS in ICU, compared to controls closely matched on severity at ICU admission; (2) to search for prognostic factors of mortality, either at ICU admission or

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during ICU stay; and (3) to assess the relative risk of death attributable to CRS after adjusting on these factors.

METHODS

A prospective, matched cohort, exposed-unexposed study was carried out from January 1, 1990, to December 31, 1995, in two ICUs in Paris, France: the 10-bed medical-surgical ICU at the Saint-Joseph Hospital and the 18-bed medical ICU at the Bichat Claude Bernard Hospital. The study design is shown in Figure 1.

Patients

Prospective ICU-wide surveillance for nosocomial infection was conducted in both units, with decisions to remove catheters and to start or stop antibiotic therapy made by the medical staff according to the following rules: catheters were removed and culture specimens obtained in the event of suspected CRS, catheter uselessness or malfunction, patient discharge from the ICU, or death. CRS was suspected in the case of (1) purulence of the catheter insertion site or (2) occurrence of fever (temperature ≥38.5°C) or hypothermia (temperature ≤36.5°C) associated with either (a) shock, erythema, or tenderness at the insertion site of the catheter in the absence of other cause of sepsis or (b) positive blood cultures. Catheter-tip specimens were processed using a simplified quantitative broth-dilution culture technique previously reported.[12] Broth cultures were subcultured onto aerobic and anaerobic agar plates, and all organisms recovered from any cultures were identified and their antibiotic susceptibility determined by standard methods. Peripheral blood cultures were obtained in the event of fever, hypothermia, or any signs of infection (eg, chills or sudden shock) and processed by the clinical microbiology laboratory according to standard methods.

All patients who developed a CRS during the study period while admitted in the ICUs comprised the eligible exposed patients for the study. The diagnosis of CRS was established when the combination of the three following criteria were fulfilled: (1) quantitative culture of catheter with $\geq 10^3$ colony-forming units/mL[13]; (2) at least one peripheral blood culture positive with the same microorganism (or two blood cultures if the microorganism was a coagulase-negative *Staphylococcus*); (3) no evidence of other infection with the same organism. A list of the 42 eligible patients was provided by the nosocomial infection files. Four were excluded because their charts could not be obtained to calculate severity indices during the ICU course. Two of these 4 patients died during their ICU stay.

The medical records of patients with CRS were reviewed, with report of age, gender, length of catheterization, and ICU and hospital lengths of stay. We also recorded for each patient, besides biological data and therapeutic management, the presence of chronic diseases based on the Acute Physiology, Age, and Chronic Health Evaluation (APACHE) II definition,[14] the severity of the underlying disease according to McCabe and Jackson's criteria (as fatal, ultimately fatal, or nonfatal),[14] the Simplified Acute Physiologic Score (SAPS) II,[15] the number of organ failures

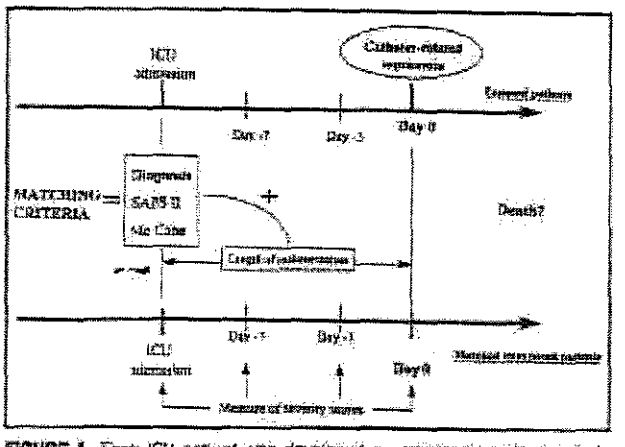

FIGURE 1. Each ICU patient who developed a catheter-related septicemia (so-called exposed patient) was matched with two unexposed patients from the same ICU, who had the same diagnosis, Simplified Acute Physiologic Score (±10) and McCabe values at ICU admission, and length of catheterization. Day 0 refers to the date of infection in exposed patients and the corresponding date at that length of catheterization in controls. Day 3 and day 7 refer to 3 or 7 days before day 0, respectively, unless patients were not already in the ICU, for whom admission score values were used. Patients were followed until hospital discharge or death. Abbreviations: ICU, intensive-care unit; SAPS II, Simplified Acute Physiologic Score II.

evaluated by the Organ System Failure (OSF) score,[16] and by the Organ Dysfunctions and Infection (ODIN) score,[17] and the Logistic Organ Dysfunction (LOD) System score.[18] These severity scores were calculated for the period within 48 hours of ICU admission, the day of the CRS (the day when the central catheter was removed, called day 0), and 3 and 7 days before the infection (respectively, day 3 and day 7; Figure 1). When the CRS occurred within the first 3 (or 7) days of ICU admission, the admission score was retained as the value of the day 3 (or day 7) score. The catheter type, as well as insertion site, time interval between catheter placement and sepsis, results of quantitative cultures, results of blood cultures, complication(s), pathogen(s), and management of catheter sepsis also were recorded.

The course of each episode of septicemia was scored as either "complicated" or "uncomplicated." Septicemia was considered uncomplicated if there were no signs of septic shock or local infection and if no evidence of metastasis to distant foci was present. Cellulitis and superficial abscess confined to the insertion site were classified as minor complications.[10] Major complications included suppuration of the blood vessel beyond the insertion site, phlebitis, endocarditis, dissemination of infection to a distant site, or septic shock.

Unexposed Patients

Assuming a mortality rate of unexposed ICU patients (ie, no CRS) with a central venous line is 30% and given that the number of exposed patients was limited to 38, the estimated number of unexposed controls needed per exposed patient to unmask a twofold increase in risk of death with a power of 80% and a type I error of 5% was 2. The medical coding files provided a list of unexposed patients with nei-

TABLE 1
CHARACTERISTICS OF THE SUBJECTS (MEAN±SD OR NUMBER AND PERCENT)

	Exposed	Unexposed	P*
Subjects	38	75	
Mean age, y	63±16	64±16	.55
Male	21 (55)	39 (52)	.74
McCabe			
Nonfatal	10 (26)	19 (25)	
Ultimately fatal <5 y	27 (71)	52 (70)	.52
Ultimately fatal <1 y	1 (3)	4 (5)	
Chronic disease	12 (32)	13 (17)	.07
Immunodeficiency	2 (5)	7 (9)	.46
Diabetes	3 (8)	3 (4)	.39
Main diagnosis			
Cardiology	2 (5)	4 (5)	
COPD	8 (21)	16 (21)	
Other pulmonary	5 (13)	10 (11)	
Other medicine	8 (21)	16 (21)	
Scheduled surgery	10 (26)	20 (26)	
Unscheduled surgery	5 (12)	10 (13)	
Cardiovascular surgery	7 (18)	13 (15)	
Digestive surgery	6 (16)	12 (16)	
Other surgery	2 (5)	4 (5)	
At ICU admission			
Transfer from other ward	27 (71)	38 (51)	.046
SAPS II	50.2±14.9	49.3±13	.45
ODIN score	2.3±1	2.4±1.1	.7
OSF score	1.2±0.9	1.4±1	.4
LOD score	6.7±3.2	6.2±3.5	.5

Abbreviations: COPD, chronic obstructive pulmonary disorder; LOD, Logistic Organ Dysfunction System; ODIN, Organ Dysfunction and Infections score; OSF, Organ System Failure score; SAPS II, Simplified Acute Physiologic Score II; SD, standard deviation.
* Wald Test or Fisher's Exact Test, as appropriate. Values are expressed as n (%) for qualitative variables, mean ± SD for quantitative variables.

ther evidence of catheter-related infection nor bloodstream infection at any time during their ICU stay.

Each patient with a CRS was then matched with two unexposed patients hospitalized from January 1990 to December 1995 in the same ICU, with respect to the following matching criteria: length of central catheterization (that ought to be in unexposed patients greater than or equal to that of the corresponding exposed patient before the diagnosis of CRS), primary diagnosis for ICU admission, predicted mortality as assessed by the SAPS II at ICU admission (±10%), and McCabe classification. In case of more than two available controls, age (±10 years) and gender were used as additional matching variables to select the two best controls.

Medical records of unexposed patients were reviewed as described above for cases. The severity scores (SAPS 2, OSF, ODIN, and LOD) also were calculated four times for each control patient: at the ICU admission; at the day of the matched case's infection (ie, when the length of central catheterization was equal to that of the corresponding case), also called D-0; and 3 and 7 days before the case's infection date (D-3 and D-7, respectively). For example, if an exposed patient had a CRS after 10 days of central venous catheterization, then day 0 for the unexposed patient would be the 10th day of catheterization; day 3 and day 7 would be the 7th and 3rd days of catheterization, respectively (Figure 1). As for the exposed patients, when the length of catheterization was less than 3 (or 7) days, severity scores at ICU admission were used for those scores.

Statistical Analysis

Characteristics of patients were compared using a two-factor analysis of variance on ranks for continuous data and using a two-covariate logistic model for qualitative data (in both cases, exposure defined one factor and the triplet—of the patient with his two controls—the second one).

Estimation of overall survival since day 0 used the Kaplan-Meier method. To compare survival between exposed and unexposed patients and to estimate a relative risk of death attributable to CRS, a multivariate generalization of the Cox model was used[19] that takes into account the correlation of the survival times of the exposed patient and the two associated unexposed patients induced by the matching.

We used two-sided tests, with P values of .05 or less denoting statistical significance. A Fortran program was used for the multivariate generalization of the Cox model,[20] and the SAS software (version 6.09; SAS Institute, Inc, Cary, NC) was used otherwise.

RESULTS

Case Study

Between January 1, 1990, and December 31, 1995, a total of 3,587 patients were admitted to the two ICUs. During this period, 42 patients developed central CRS, for an estimated incidence of 11.7 per 1,000 ICU admissions. Four of the 42 patients were excluded because their charts could not be obtained. The main characteristics of the remaining 38 patients at ICU admission are shown in Table 1. Twenty-three cases were medical patients, and 15 were surgical patients.

The mean (± standard deviation) duration from ICU admission to diagnosis of CRS was 16.8±9.6 days. The mean duration of central catheterization before the infection was 17.1±9.6 days, and the mean duration of central catheterization with the infecting catheter before the infection was 9.5±6.8 (range, 2-30) days.

Forty-three microorganisms responsible for CRS were isolated: *Staphylococcus aureus* (21), coagulase-negative *Staphylococcus* (2), *Streptococcus* species (1), *Acinetobacter baumannii* (2), *Klebsiella pneumoniae* (6), *Pseudomonas aeruginosa* (8), *Escherichia coli* (1), *Proteus* species (1), and *Candida albicans* (1). Five infections were polymicrobial. Of *S aureus* isolates, 18 were resistant to methicillin. Five of the 6 strains of *K pneumoniae* produced extended-spectrum β-lactamases. The median number of positive blood cultures

was 4. The median duration of positive blood cultures after catheter withdrawal was 1 day. At the time of catheter removal, 18 patients received antimicrobial therapy for various other reasons. Microorganisms recovered from catheter cultures never were susceptible to the previous antimicrobial therapy.

Of the 38 patients, 29 received appropriate therapy immediately after catheter removal, 1 died from septic shock before the results of blood culture was known and without receiving effective antimicrobials, and the 8 remaining patients were given delayed appropriate therapy, once susceptibility test results were available.

Complications occurred in 33 of 38 patients, including major events in 29 (Table 2). Between 7 days before the infection and day of infection, the mean of SAPS II and of the LOD scores increased by 12 and 1.8 points, respectively ($P<.001$; Figure 2). Intensive-care–unit mortality was 62% for *S aureus* bacteremia and 36% for bacteremia involving other microorganisms ($P=.14$). Intensive-care–unit mortality was not different between patients appropriately and inappropriately treated.

Exposed-Unexposed Matched Cohort

Matching. Of 3,587 patients hospitalized in the same ICU during the study period, 403 possible controls were identified based on the main diagnosis at ICU admission, the absence of catheter-related infection, and the absence of bacteremia. All exposed patients but 1 were matched successfully with 2 unexposed controls; the remaining exposed patient, with 49 days of central catheterization, could be matched successfully with only 1 unexposed patient. The main characteristics of exposed and unexposed patients are shown in Table 1. All severity scores measured in the exposed group at the time of infection were significantly higher than those of unexposed patients at the corresponding day of catheterization (Figure 2). While the mean severity score decreased from ICU admission to day 0 in unexposed patients, it was stable or even slightly increased in the exposed group.

Twenty (54%) and 52 (70%) nosocomial infections occurred between ICU admission and day 0 in exposed and unexposed patients, respectively. The rate of nosocomial infections ($P=.15$) and the rate of nosocomial pneumonias ($P=.12$) before day 0 did not differ for exposed and unexposed patients.

Survival. Nineteen of the 38 cases died in ICU, representing a crude ICU mortality rate of 50.0% (95% confidence interval [CI_{95}], 34.1%-65.9%); 16 unexposed patients died in ICU, for a mortality rate of 21.3% (CI_{95}, 11.3%-31.3%). The observed hospital mortality was 52.6% (CI_{95}, 36.7%-68.5%) in exposed patients, substantially above the hospital mortality rate observed in unexposed patients, 27% (CI_{95}, 17%-37%; $P=.007$).

The hospital mortality of exposed patients was higher, although nonsignificantly, than the expected mortality as predicted by SAPS II (45.3%) or by the LOD score at ICU admission (35.4%). In contrast, the observed mortality of the nonexposed group was lower than the expected mortality as predicted by the SAPS II (observed, 27%; expected, 43%; $P=.05$). For eight deaths (21%), the physicians in charge of the patient considered that the CRS was the main cause of death.

Based on ICU survival rates, the risk of death was

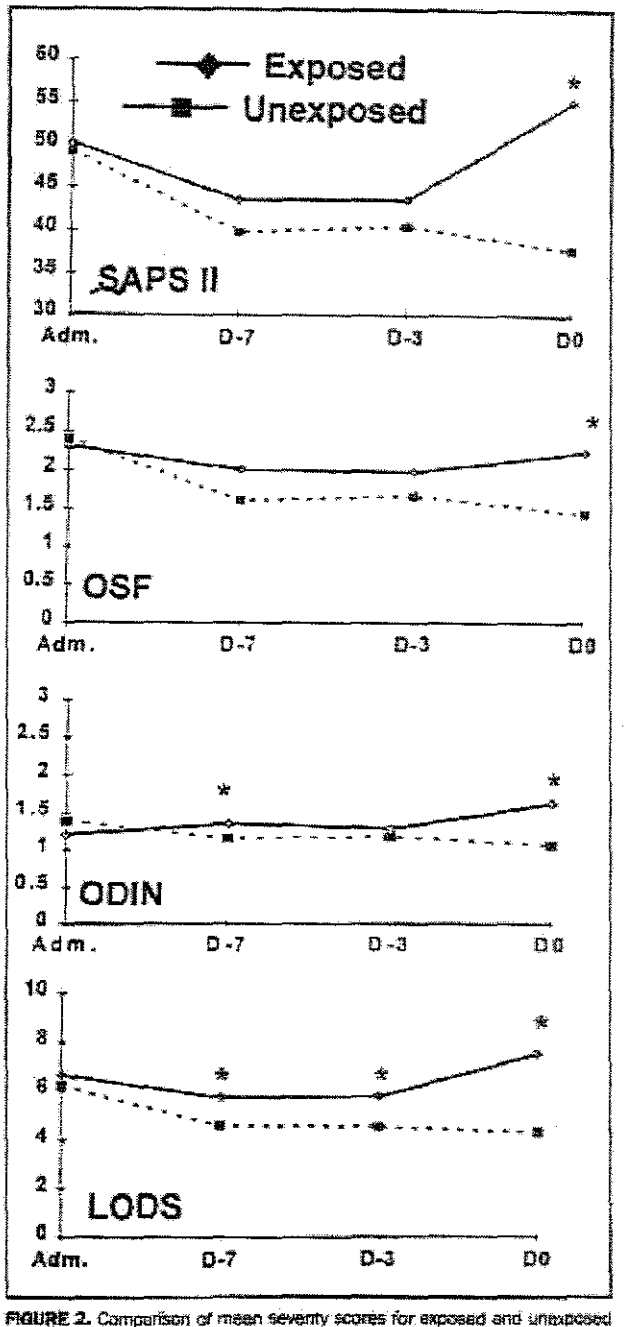

FIGURE 2. Comparison of mean severity scores for exposed and unexposed patients. From intensive-care–unit admission to date of infection, the mean value of all severity scores tended to increase in the exposed infected patients, whereas it was roughly unchanged in the unexposed patients. The asterisks mark significant differences between exposed and unexposed patients ($P<.05$). Abbreviations: Adm, admission; D0, day 0; D3, day 3; D7, day 7; LODS, Logistic Organ Dysfunction System; ODIN, Organ Dysfunction and Infection score; OSF, Organ System Failure score; SAPS II, Simplified Acute Physiologic Score II.

TABLE 2
COMPLICATIONS OF CATHETER-RELATED SEPTICEMIA

Complications*	No. (%) of Episodes
None	5 (13.8)
Minor	4 (10.5)
Major	29 (76.3)
Severe sepsis	23 (60.5)
Septic shock	20 (52.6)
Suppurative thrombophlebitis	10 (26.3)
Metastatic infections†	12 (31.6)
Endocarditis	3 (7.9)
Death due to CRS‡	8 (21)
Death in the first week after CRS	10 (26.3)

Abbreviation: CRS, catheter-related septicemia.
* See text for definitions.
† Pneumonia, 3; pleura, 1; sinus, 1; other catheter, 3; urinary tract, 1; arthritis, 1; intra-abdominal abscess, 2.
‡ The physicians in charge of the patient considered that CRS directly contributed to the patient's death.

TABLE 3
ESTIMATED EXCESS MORTALITY DUE TO CATHETER-RELATED SEPTICEMIA

Model	RR	CI_{95}	P*
Unadjusted	2.06	1.16-3.68	.01
Adjusted for prognostic variables at ICU admission	2.01	1.08-3.73	.03
Adjusted for prognostic variables before day 3	1.41	0.76-2.61	.27
Adjusted for prognostic variables, including those assessed at day 3	1.3	0.69-2.46	.42

Abbreviations: CI_{95}, 95% confidence interval; RR, relative risk.
* Wald test.

significantly increased in exposed as compared to unexposed patients, with a relative risk (RR) of 2.06 (CI_{95}, 1.16-3.68; P=.01; Table 3). The estimated relative risk of death was then adjusted on risk factors, as assessed at ICU admission and during the follow-up, both with and without information gathered at D-3 (possibly reflecting the underlying but undiagnosed bacteremia). The multivariable Cox model found age, chronic disease, the LOD score at D-7, and the SAPS II at D-3 to be significantly associated with outcome (Table 3).

Adjustment on these prognostic covariates markedly modified the results; the estimated adjusted relative risk of death of exposed over unexposed patients was not significantly different from 1, whether the information gathered at D-3 was incorporated in the model (RR, 1.3; CI_{95}, 0.63-2.46; P=.42) or not (RR, 1.4; CI_{95}, 0.76-2.6; P=.27).

DISCUSSION

This study was conducted to assess the attributable morbidity and mortality of ICU CRS, using a cohort design. We focused on the estimation of the relative risk of death in patients with CRS (exposed patients) compared to that of similar but unexposed patients, using a matched exposed-unexposed design. This allowed us to distinguish the mortality attributable to CRS from that unrelated to CRS, by matching on the prognostic information collected at ICU admission and the duration of exposure.

The risk of ICU death in patients with CRS was estimated to be an approximately twofold increase compared to that of unexposed patients. Adjusting for all prognostic information collected at ICU admission did not modify the results (Table 3). Moreover, CRS was associated with a substantial observed morbidity. More than two thirds of these episodes were associated with severe sepsis or septic shock. This finding is in accordance with data of Giraud and coworkers,[21] who classified eight of nine CRSs as major iatrogenic events. This likely is explained, at least partially, by the low incidence of coagulase-negative staphylococci bacteremia in our series, with *S aureus* being the most frequently isolated gram-positive organism in both centers. This result is in opposition to some series in which coagulase-negative staphylococci represented most of the recovered gram-positive cocci,[6] but in accordance with others.[3,12,22,23] In the latter series, coagulase-negative staphylococcal CRS was rare, whereas catheter colonization with the same microorganism was frequent. Another possible explanation of these results is the high prevalence of methicillin-resistant *S aureus* in European hospitals and particularly in France.[24] This abnormal colonizing cutaneous flora may have replaced the normal coagulase-negative staphylococci (CNS) and thus may have increased the risk of *S aureus* catheter-related infection. However, we cannot exclude that a large fraction of CNS bacteremia went undiagnosed because of the absence of clinical signs of sepsis[7] and subsequent blood cultures. Only 12.4% of blood cultures positive for CNS have been found to be clinically important in a previous report.[25] Finally, the incidence of CRS in this series could have been falsely reduced by the requirement for at least two positive blood cultures to diagnose coagulase-negative staphylococcal septicemia. These factors could limit the generalizability of our results.

However, the main result of this study is that the attributable mortality of CRS was markedly modified by the incorporation of prognostic information gathered during the ICU stay, even when excluding the information on severity 3 days before infection (day 3 severity scores might have been influenced by the incubation phase of the infectious process in exposed patients); in either case, the risk of death in exposed patients was no longer significantly different from that of unexposed patients. The attending physicians considered that CRS was the immediate cause of death of eight patients (Table 2); our results suggest that, had these patients not died of CRS, many of them would have been expected to have died from other causes.

Our results do not support the initial hypothesis of a twofold increased risk of mortality attributable to CRS, but are consistent with a relatively smaller influence of CRS on

mortality. We can make no definite conclusion on this point because of the relatively small number of events studied, but the final relative risk of death of 1.41 is consistent with a 10% to 20% increased mortality associated with CRS.

Our results suggest that the increased mortality observed in patients who developed CRS is explained mostly by increasing severity of their illness before infection. This is seen in Figure 2, which shows a less favorable course of severity scores after ICU admission in CRS patients than in unexposed patients. Persistent organ failures and severity of patients probably put them at higher risk of subsequent infection.[26]

These data raise difficult questions about the limits of exposed-unexposed studies in unmasking risk of death of nosocomial events in critically ill patients. The exact role that nosocomial infections play in worsening the outcome of ICU patients is difficult to assess. In critically ill patients whose clinical status is severe enough to require intensive care, death is frequent and due to various causes. Thus, although the rates of nosocomial infection and mortality in the ICU are high, the assessment of responsibility among several shared risk factors that confound the relationship remains difficult. Adjustments using only baseline information probably are inaccurate, because they do not take into account the risk course during the ICU stay. Similarly, a previous report from our group about nosocomial pneumonia in the ICU showed that, although nosocomial pneumonia was associated with a twofold increase in the risk of death, patients suspected to have nosocomial pneumonia had a mortality similar to patients in whom pneumonia was demonstrated.[27]

One may question the accuracy of adjustments using either severity or organ dysfunction scores calculated during the ICU stay, as these scores were constructed from data collected on the first day of the ICU stay. Predicted mortality as assessed by SAPS II and LOD were different, reflecting the poor accuracy of this kind of severity scores in predicting death of a particular subgroup of ICU patients. However, previously published studies[28,29] showed that an increase in the APACHE II score after nosocomial bacteremia significantly correlates with outcome.

To conclude, the present study showed that severity of illness before the onset of bacteremia is related closely to the risk of death, independently of severity at admission and occurrence of bacteremia. This result strongly argues for the incorporation of ICU-course severity trends in any analyses of the risk of mortality due to iatrogenic events.

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ANNEXE 5

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ORIGINAL

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Mortality associated with late-onset pneumonia in the intensive care unit: results of a multi-center cohort study

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Abstract *Objective*: To evaluate the attributable mortality associated with late-onset nosocomial pneumonia (LOP) while taking into account the severity at admission, the evolution of the patients during the first 4 days after admission to the ICU and the appropriateness of initial empiric antibiotic treatment. *Design*: Multicenter cohort study with prospective standardization of diagnostic interventions when nosocomial pneumonia develops. *Setting*: Medical and surgical ICUs of four university-affiliated teaching hospitals. *Patients*: Seven hundred sixty-four consecutive patients requiring ICU hospitalization for at least 4 days. *Main outcome measures*: The clinical and biological data as well as the therapeutic data and the outcome were prospectively recorded from the day of admission to ICU discharge. Simplified Acute Physiologic Score (SAPS II) and Logistic Organ Dysfunction (LOD) score were collected and computed within the first 4 calendar days of ICU admission. Variables associated with the outcome were selected using a stepwise Cox model. The time to acquisition of the first LOP was then introduced in the final model as a time-dependent covariate. The analysis was stratified by ICU center. Finally, as initial antibiotic therapy could have an impact on the increased risk of death induced by LOP, the Cox model was applied again introducing LOP immediately adequately treated and LOP not immediately adequately treated as two different time-dependent covariates. *Results*: Late-onset pneumonia developed in 89 patients (12%). A McCabe score of more than 1, SAPS II score and increases in SAPS between days 1 and 2, days 2 and 3, and days 3 and 4 were significantly associated with an increased risk of death. When the time to acquisition of the first episode of LOP was introduced into the Cox model, the LOP occurrence was associated with increased mortality, even adjusted over the selected prognostic parameters and after stratification by center (hazard ratio (HR)=1.53, 95% CI 1.02–2.3, p=0.04). When LOP immediately adequately treated and LOP not immediately adequately treated were separately introduced into the Cox model, inappropriately treated LOP remained significantly associated with an increased risk of mortality (HR=1.69, 95% CI 1.08–2.65, p=0.022), whereas appropriately treated LOP did not (HR=1.44, 95% CI 0.75–2.76, p=0.27). *Conclusion*: These data suggest that, in addition to severity scores, the underlying medical conditions and the evolution of severity within the first 4 days in ICU, late-onset pneumonia independently contribute to ICU patient mortality when empirical antibiotic treatment is not immediately appropriate.

Keywords Multicenter · Attributable mortality · Late-onset pneumonia · Nosocomial pneumonia · Adequate or inadequate antibiotic treatment

Introduction

The extra mortality induced by nosocomial pneumonia in ventilated patients remains a controversial issue in the literature. Previous studies have reached conflicting conclusions regarding whether the severity of the underlying illness or the development of nosocomial pneumonia was the most highly predictive factor of a poor outcome and of prolonged hospitalization [1, 2, 3]. Variables that may influence the extent to which nosocomial pneumonia increases morbidity or mortality include the patient population affected, timing of the onset of pneumonia, diagnostic strategy, causative organism and adequacy of initial therapy. For example, several studies have suggested that specific microorganisms responsible for ventilator-associated pneumonia (e.g., *Pseudomonas aeruginosa* or *Acinetobacter* species) were important determinants of patient outcome [4, 5, 6].

It has also been demonstrated that in pneumonia occurring more than 96 h after ICU admission, namely late-onset pneumonia (LOP), there was an increased likelihood of infection with resistant gram-negative organisms including *Pseudomonas aeruginosa* and *Acinetobacter* species [7, 8]. Then LOP may carry a high risk of mortality and morbidity, probably because cases are often caused by resistant organisms which are difficult to treat, and may result in delayed or ineffective antibiotic therapy. However, LOP occurred in patients staying in the ICU for days, often with persistent very high severity of illness and this could be a very important confounding factor. We therefore performed a prospective study to evaluate risk factors for death in patients admitted to an ICU for more than 96 h, and particularly the association between LOP and mortality. Our particular concern was to take into account illness severity on admission, but also daily variation of illness severity within the first 4 days on the ICU and appropriateness of initial empiric antibiotic treatment, in evaluating the specific attributable mortality associated with pneumonia.

Methods

Criteria for eligibility

This study was conducted during an 18-month period within the medical and surgical ICUs of four university-affiliated teaching hospitals: one medical ICU in Hôpital Louis Mourier (Colombes, France), two medical-surgical ICUs in Hôpital Saint Joseph (Paris, France) and in Hôpital Avicenne (Bobigny, France), and one surgical ICU in Hôpital Antoine Béclère (Clamart, France). Consecutive patients older than 16 years and hospitalized in the ICU for at least 5 calendar days were eligible for the study.

Data collection and baseline data

During the study period (January, 1997 to July, 1998), all the patients hospitalized for more than 48 h in ICU were followed for the appearance of nosocomial infections. In those patients, we recorded prospectively the clinical and biological data as well as the therapeutic data from the day of admission to ICU discharge. The investigators were particularly involved in the data base creation. All codes and definitions were created prior to the study start. Senior physicians completed report forms. Another investigator reviewed all the report forms before they were keyed. For each patient, standardized forms were completed at ICU admission and daily until ICU discharge or death. The following data were recorded: diagnosis, main clinical features and laboratory findings, treatment modalities, especially respiratory support, antimicrobial treatments, nosocomial pneumonia and outcome. From the data collected within the first 4 calendar days (Ds) of ICU admission, the Simplified Acute Physiologic Score (SAPS II) [9] and the Logistic Organ Dysfunction (LOD) score [10] were computed. Chronic health status was assessed using the Knaus classification [11]. McCabe score [12] was also recorded. Diagnosis of nosocomial pneumonia was reported together with the results of microbiological tests from the protected distal samples. All changes in the clinical and therapeutic course were recorded. Only those patients hospitalized in a ICU for at least 5 calendar days were entered in this study.

Late-onset pneumonia

At the beginning of the study investigators decided to use the same following definitions of nosocomial pneumonia: LOP (occurring more than 96 h after admission) [6, 7, 13] was suspected by the staff physicians according to the appearance of persistent pulmonary infiltrates on the chest X-ray and at least one of the following clinical or biological findings [14]: (1) purulent tracheal secretions, (2) body temperature higher than 38.5°C or lower than 36.5°C, (3) white blood cell count more than 10×10^9/l or less than 4×10^9/l. When pneumonia was suspected, fiberoptic bronchoscopy with protected specimen brush and/or bronchoalveolar lavage or single-sheeted blind plugged telescopic catheter were performed for each patient [15, 16, 17, 18]. Confirmed LOP was defined, according to the recommendations of the First International Consensus Conference on the Clinical Investigation of Ventilator Associated Pneumonia [19], by a positive protected specimen brush ($\geq10^3$ cfu/ml), by a positive plugged telescopic catheter ($\geq10^3$ cfu/ml) or by a positive culture of bronchoalveolar lavage fluid ($\geq10^4$ cfu/ml). None of the patients received any new antimicrobials before respiratory bacteriological procedures. Previous antibiotic use was defined as antibiotic administration for more than 48 h prior to the suspicion of pneumonia.

Therapeutic decisions were left to the discretion of the attending physicians and discussed daily with the medical staff in each center. No common therapeutic regimens were recommended in any case. When infection was strongly suspected because of clinical signs of severe sepsis and/or septic shock, the patient's physician prescribed empiric antimicrobial therapy without delay. Treatment was further adapted or ordered according to the results of bacterial pulmonary cultures, susceptibility testing of antimicrobials and/or clinical response. An "uncovered" microorganism was considered when an isolated microorganism was not susceptible to any of the antibiotics administered. Inappropriate initial antibiotic treatment was defined by the isolation of at least one pathogen with a significant threshold in the bacteriological samples resistant or intermediate to the antibiotics prescribed. All patients were monitored until their discharge from the hospital and changes in the clinical and therapeutic course were recorded.

Statistical analysis

Patients with and without LOP were compared using Mann Whitney or Fischer exact test, as appropriate. A stepwise logistic regression was computed to select independent risk factors for LOP.

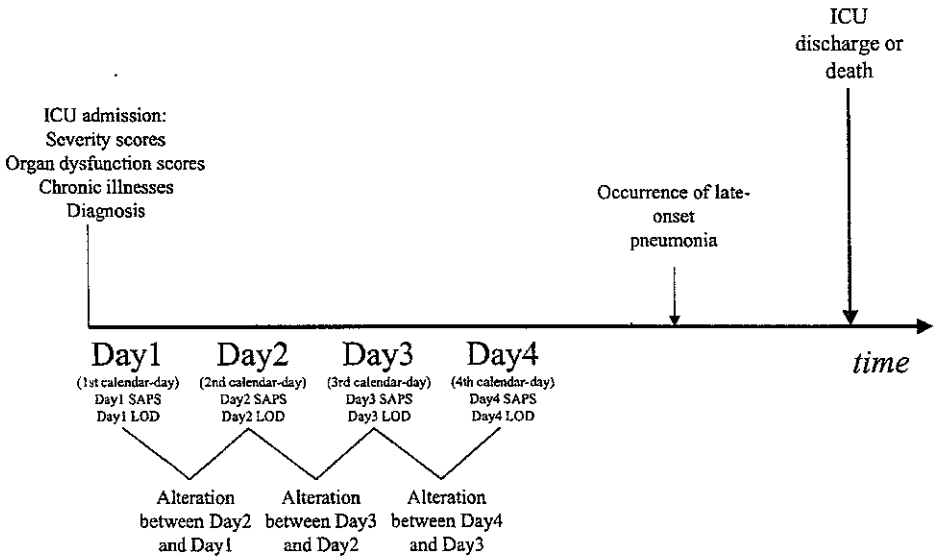

Fig. 1 Study design: the occurrence of ICU discharge or death defined the end point. Prognostic covariates were measured at admission. Severity scores were computed during the first 4 calendar days. Alteration of scores between consecutive calendar days: when a score increased, it was given the value of 1, otherwise the value was 0. Finally, the time to acquisition of late-onset pneumonia was introduced as a time-dependent covariate in the model

The main end point was the overall survival from the date of inclusion (the 5th calendar day after ICU admission). Patients who were discharged alive from the ICU were no further evaluated after their discharge. The Kaplan-Meier estimate of survival was computed. We first studied the prognostic value for death of several baseline characteristics, assessed within the first 5 days of ICU admission, including demographic characteristics (age, sex, chronic underlying disease, history of COPD, associated neoplasm, associated immunosuppression and McCabe score), cause of ICU admission and diagnosis severity of the patients on admission (SAPS II, LOD score, Glasgow coma scale), severity of the patients' conditions within the first 4 calendar days (SAPS II and LOD score were computed daily), and severity alterations (SAPS II and LOD score alterations between days 1 (D1) and 2 (D2), days 2 and 3 (D3), and days 3 and 4 (D4)) (Fig. 1). All variables were introduced as dummy variables except SAPS II (after checking for log-linearity assumption).

Score alterations rather than daily scores were introduced into the model at the first step to avoid over-fitting. Only the directions of changes were included on the basis of the non-parametric modeling using generalized additive proportional hazard (PH) models [20]. According to the plot of the estimated functions for each score alteration using smoothing splines, the direction of change was the most important predictor to delineate two groups of interest (low- and high-risk groups). Alteration of severity scores took the value "1" when scores increased and the value "0" otherwise. Search for prognostic factors was based on the log-rank test, which compares the distribution of survival times in several subsets. Variables found to be associated with the outcome by the log-rank test at the 5% level, i.e., influencing the survival time, were then entered into a Cox model. Severity score alteration instead of days 1–4 severity scores were used to avoid over-fitting. A backward procedure allowed for sequentially selecting the variables that were significantly related to the outcome, as tested by the likelihood ratio test at the 5% level. Thus, variables that did not add predictive information to the remainders were not kept in the model. Hazard ratios were computed (with 95% confidence interval) and were used to measure relative risk.

As a second step, the time to acquisition of the first LOP was introduced in the final model as a time-dependent covariate. The analysis was stratified by center, as ICU mortality and LOP incidence were different among the centers. The Gail and Simon test was used to evaluate the interaction between HR of mortality associated with nosocomial pneumonia and center [21]. Finally, as initial antibiotic therapy could have an impact on the extra risk of death induced by LOP, the Cox model was applied again while LOP immediately adequately treated and LOP not immediately adequately treated were introduced simultaneously as two time-dependent covariates. Levels of significance were represented by p values derived from two-sided tests. A p value of 0.05 or less

Table 1 Patients' characteristics at admission and within the first 24 h after admission (n=764) (*COPD* chronic obstructive pulmonary disease)

	Number (%) or mean (SD)
Age (years; mean ± SD)	63±17
Sex M/F, *n* (%)	460 (60)/ 304 (40)
Diagnosis, *n* (%)	
COPD	68 (9)
Other pulmonary	275 (36)
Cardiology	166 (22)
Neurology	100 (13)
Other medical specialty	134 (18)
Digestive surgery	201 (26)
Other surgery	79 (10)
Trauma	26 (3)
Diagnostic category, *n* (%)	
Scheduled surgery	72 (9)
Emergency surgery	159 (21)
Medical	533 (70)
SAPS II, mean ± SD	42±10
MacCabe score, *n* (%)	
≥5 years	388 (51)
<5 years	287 (37)
<1 year	89 (12)
Chronic illness, *n* (%)	375 (49)
Previous history of COPD, *n* (%)	68 (9)
Immunosuppression, *n* (%)	107 (14)
Septic shock/other shock at admission, *n* (%)	66 (9)/ 79 (10)
Pneumonia at admission, *n* (%)	148 (19)
Acute renal failure at admission, *n* (%)	48 (6)
Glasgow coma score <8 at admission, *n* (%)	94 (12)
Admission from other units, *n* (%)	398 (52)

Table 2 Characteristics of the patients with late-onset nosocomial pneumonia[a] (*LOD* logistic organ dysfunction, *D* day)

	Patients with late-onset pneumonia n=89	Patients without late-onset pneumonia n=675	p values
Age (year)	66±14	62±18	0.05
Sex M/F	66(74)/23(26)	394(58)/281(42)	0.5
Admission diagnosis			
Medicine	60 (67)	473 (70)	0.2
Scheduled surgery	5 (6)	67 (10)	
Emergency surgery	24 (27)	135 (20)	
SAPS II score	45±13	41±18	0.02
SAPS D1	40±14	37±16	0.1
SAPS D2	39±12	33±16	<0.0001
Increase in SAPS between D1 and D2[b]	42 (47)	204 (30)	0.002
SAPS D3	37±12	32±16	<0.0001
Increase in SAPS between D2 and D3[b]	27 (30)	215 (32)	0.8
SAPS D4	36±12	31±17	<0.0001
Increase in SAPS between D3 and D4[b]	30 (34)	222 (33)	0.9
SAPS D5	36±11	32±18	<0.0001
LOD score D1	4.5±2.8	3.7±2.8	0.005
LOD score D2	4.2±2.2	3.3±2.5	<0.0001
Increase in LOD score between D1 and D2[c]	29 (33)	164 (24)	0.09
LOD score D3	4.1±2.5	3.0±2.5	<0.0001
Increase in LOD score between D2 and D3[c]	23 (26)	164 (24)	0.8
LOD score D4	4.1±2.4	3.0±2.6	<0.0001
Increase in LOD score between D3 and D4[c]	22 (25)	168 (25)	0.9
LOD score D5	3.9±2.1	3.2±3.0	0.0003
MacCabe score >1	50 (56)	326 (48)	0.2
Chronic illness	47 (56)	328 (48)	0.5
Previous history of COPD	20 (22)	48 (7)	0.001
Immunosuppression	12 (13.5)	95 (14)	0.6
At admission			
Septic shock	11(12)	65 (10)	0.5
Other shock	9(10)	91 (13)	0.4
Pneumonia	35 (39)	126 (19)	0.00012
Coma	14 (15)	77 (11)	0.5
Admission from other units	51 (57)	320 (47)	0.09
Days in ICU when pneumonia developed	12±10	NA	–
Duration of mechanical ventilation	27.5±20	7.3±11	<0.0001
Length of ICU stay	33±24	12±13	<0.0001
Total length of hospital stay	52±34	30±28	<0.0001
Expected probability of death according to SAPS II	36±24	33±28	0.8
ICU deaths	42 (47)	146 (22)	<0.0001
Hospital deaths	50 (56)	189 (28)	<0.0001

[a] Values are reported as means ± SD and n (%) for quantitative and qualitative variables, respectively. Comparison was performed using Mann-Whitney or Fisher exact test as appropriate

[b] Number of patients who had an increase in SAPS II within the first 4 days post-admission in ICU – i.e. between D1 and D2, D2 and D3, and D3 and D4

[c] Number of patients who had an increase in LOD score within the first 4 days post-admission in ICU – i.e. between D1 and D2, D2 and D3 and D3 and D4

was considered to indicate statistical significance. Statistical analysis was performed using SAS (Statistical Analysis System, Carey, N.C.) software package.

Results

Population

A total of 764 patients requiring ICU hospitalization for at least 5 calendar days were consecutively admitted to the four different ICUs. Patients' baseline characteristics are shown in Table 1. Eighty percent of these patients required mechanical ventilation within the first 24 h after admission. The median duration of ICU stay and hospital stay was 9 days (range 5–126) and 24 days (range 5–249), respectively.

Late-onset pneumonia

Late-onset pneumonia developed in 89 patients (12%). In 69 (77.5%) cases, it occurred 7 days or more post-admission. The general characteristics of this population

Table 3 Microorganisms recovered from first episodes of late-onset pneumonia

Gram-positive	36
Staphylococcus aureus (SA)	19
Oxacillin-sensitive SA	5
Oxacillin-resistant SA	14
Coagulase negative *Staphylococcus*	8
Streptococcus pneumoniae	1
Streptococcus species	6
Other Gram-positive	2
Gram-negative bacteria (GNB)	71
Haemophilus species	8
Pseudomonas aeruginosa/species	27/1
Acinetobacter baumannii	1
Escherichia coli	9
Enterobacter cloacae	7
Klebsiella species	5
Other *Enterobacteriaceae* / GNB	6/7
Anaerobes	1
Candida/yeast	2
Total (microorganisms/episodes)	110/89

and the selected risk factors for the occurrence of LOP in univariable analysis are shown in Table 2. Of the variables selected, two remained significantly associated with the occurrence of LOP in the multivariable analysis: pneumonia at admission (odds ratio (OR)=2.79, 95% CI 1.42–3.65; p=0.0006) and a median LOD score at D2 greater than 4 (OR=2.58, 95% CI 1.65–4.05; $p<10^{-4}$).

At the time of the LOP suspicion, 50 of the 89 patients had already received antimicrobials (amoxicillin: 10; amoxicillin/clavulanate: 10; third generation cephalosporins: 9; ureidopenicillin: 4; imipenem: 2; aminoglycosides: 4; fluoroquinolones: 10; glycopeptides: 7; macrolides: 6; metronidazole: 5; fluconazole: 7; other: 6).

One hundred ten organisms were recovered from the protected distal samples of patients with LOP (Table 3). The initial antibiotic treatment was with one antibiotic in 11 cases, with two in 34 cases and consisted of three or more antibiotics in other cases. The initial empiric antibiotic therapy instituted was considered immediately effective or appropriate in 34/89 cases (38%). It was effective in 60/89 (68%) cases in the first 24 h.

The overall ICU mortality of the total population (i.e., requiring ICU hospitalization for at least 5 calendar days) was 25% (188 deaths). Overall ICU mortality was 47% among LOP patients and 22% among patients without episodes of LOP. The standard mortality ratio was 1.55 for LOP patients and 0.84 for patients without episodes of LOP.

Prognostic analyses

Table 4 summarizes the results of the univariable prognostic analyses. Other covariates, (particularly previous history of COPD and pneumonia at admission) were not associated with ICU death. Of the variables selected as prognostic by the log-rank test, five remained significantly associated with a poor outcome in the final Cox model: McCabe score more than 1, SAPS II and increases in SAPS between D1 and D2, D2 and D3, and D3 and D4 (Table 5). When the occurrence of the first episode of LOP was introduced into the Cox model as a time-dependent binary covariate, it was associated with an increased risk of mortality, even adjusted over the selected prognostic parameters and after stratification by center (HR=1.53, 95% CI 1.02–2.3, p=0.04). When LOP immediately adequately treated and LOP not immediately adequately treated were separately introduced into the Cox

Table 4 Prognostic factors of patients hospitalized in ICU for more than 96 h (univariate analysis)[a]

	Number of deaths n=188	Number of patients alive n=576	p (log-rank test)
Age (years)	68±15	61±18	$<10^{-4}$
MacCabe score >1	128 (68)	248 (43)	$<10^{-4}$
Chronic illness	119 (63)	256 (44)	$<10^{-4}$
Immunosuppression	37 (20)	70 (12)	0.02
SAPS II score	52±18	25±16	$<10^{-4}$
SAPS D1	43±17	29±13	$<10^{-4}$
SAPS D2	44±20	27±13	$<10^{-4}$
SAPS D3	44±20	26±14	$<10^{-4}$
Increase in SAPS between D1 and D2[b]	88 (47)	166 (29)	0.0006
Increase in SAPS between D2 and D3[b]	73 (39)	169 (29)	0.02
Increase in SAPS between D3 and D4[b]	80 (43)	172 (30)	0.0017
LOD score D1	4.7±2.9	2.5±2.0	$<10^{-4}$
LOD score D2	5.1±3.5	2.2±2.0	$<10^{-4}$
LOD score D3	5.1±3.3	2.2±2.0	$<10^{-4}$
Increase in LOD score between D1 and D2[c]	61 (32)	129 (22)	0.0017
Increase in LOD score between D2 and D3[c]	66 (35)	121 (21)	0.0019
Increase in LOD score between D3 and D4[c]	64 (34)	126 (22)	0.0018
Admission from other units	100 (53)	271 (47)	0.002

[a] Values are reported as means ± SD and n (%) for quantitative and qualitative variables, respectively

[b] Number of patients who had an increase in SAPS II within the first 4 days post-admission in ICU – i.e. between D1 and D2, D2 and D3 and D3 and D4

[c] Number of patients who had an increase in LOD score within the first 4 days post-admission in ICU – i.e. between D1 and D2, D2 and D3 and D3 and D4

Table 5 Prognostic factors of patients hospitalized in ICU more than at least 5 calendar days (multivariable analysis)[a] (*HR* hazard ratio, *CI* confidence interval)

	First model[b]		Second model[c]	
	p value	HR (95% CI)	*p* value	HR (95% CI)
MacCabe score >1	$<10^{-4}$	2.43 (1.72–3.44)	$<10^{-4}$	2.12 (1.51–2.99)
SAPS II score	$<10^{-4}$	1.03 (1.02–1.04)	$<10^{-4}$	1.03 (1.02–1.04)
Increase in SAPS between D1 and D2[d]	0.004	1.56 (1.16–2.11)	$<10^{-4}$	2.01 (1.48–2.74)
Increase in SAPS between D2 and D3[d]	$<10^{-4}$	1.84 (1.40–2.50)	$<10^{-4}$	1.97 (1.44–2.69)
Increase in SAPS between D3 and D4[d]	$<10^{-4}$	1.80 (1.33–2.44)	0.004	1.56 (1.16–2.11)
Late-onset pneumonia occurrence[b]	0.04	1.54 (1.10–2.30)	–	–
Late-onset pneumonia appropriately treated[c]	–	–	0.27	1.44 (0.75–2.76)
Late-onset pneumonia inappropriately treated[c]	–	–	0.022	1.69 (1.08–2.65)

[a] All variables significant in the univariate analysis were introduced into a Cox model. To avoid over-fitting, score alterations rather than daily scores were introduced in the multivariate model at the first step. Analysis was stratified by center

[b] The acquisition of the first nosocomial pneumonia was introduced in the first final model as a time-dependent covariate simultaneously with the five previously selected covariates

[c] As initial antibiotic therapy could have an impact on the increased risk of death induced by LOP, the Cox model was applied again while introducing LOP immediately adequately treated and LOP not immediately adequately treated as two different time-dependent covariates (second model)

[d] Number of patients who had an increase in SAPS II within the first 4 calendar days in ICU – i.e. between D1 and D2, D2 and D3 and D3 and D4

Table 6 Baseline characteristics and crude outcomes of the four ICU populations

ICUs, centers	I *n*=235	II *n*=245	III *n*=93	IV *n*=191	*p*
Age (years; mean ± SD)	66±16	64±17	59±23	60±16	0.003
Diagnosis, *n* (%)					$<10^{-4}$
MOF/shock	65 (28)	48 (20)	29 (31)	32 (16)	
Acute respiratory failure	82 (35)	93 (38)	11 (12)	81 (42)	
COPD exacerbation	28 (12)	35 (14)	1 (1)	4 (2)	
Acute renal failure	11 (5)	15 (6)	11 (12)	11 (6)	
Coma	31 (13)	34 (14)	6 (6)	22 (12)	
Trauma	1 (0.4)	1 (0.4)	9 (10)	3 (2)	
Other	17 (7)	19 (8)	26 (28)	38 (20)	
Diagnostic category, *n* (%)					$<10^{-4}$
Medical	153 (65)	210 (86)	33 (35)	137 (72)	
Scheduled surgery	32 (14)	4 (2)	11 (12)	25 (13)	
Emergency surgery	50 (21)	31 (13)	49 (53)	29 (15)	
SAPS II (mean ± SD)	41.3±15	44±16	33±16	46±9	$<10^{-4}$
MacCabe score, *n* (%)					$<10^{-4}$
≥5 years	72 (30)	129 (53)	72 (77)	115 (60)	
<5 years	144 (61)	83 (34)	13 (14)	47 (25)	
<1 year	19 (9)	33 (13)	8 (9)	29 (15)	
Chronic illness[a], *n* (%)					$<10^{-4}$
None	113 (48)	108 (44)	64 (69)	104 (54)	
Respiratory	54 (23)	68 (28)	7 (8)	31 (16)	
Cardiac	42 (18)	39 (16)	2 (2)	9 (5)	
Hepatic	12 (5)	19 (8)	15 (16)	12 (6)	
Immunosuppression	27 (11)	32 (13)	8 (9)	40 (21)	
Pneumonia at admission, *n* (%)	53 (22.5)	64 (26.1)	6 (6.4)	38 (19.8)	10^{-4}
Admission from other units, *n* (%)	135 (58)	100 (41)	57 (61)	74 (39)	10^{-4}
Duration of mechanical ventilation (days)	13±14	10±16	6±13	7±11	$<10^{-4}$
Length of stay in ICU (days)	16±17	14 ±16	14.±20	12±12	0.6
Total length of stay in hospital (days)	36±31	33±34	33±30	28±21	0.3
ICU/hospital mortality rates (%)	28/38	17/25	25/33	30/34	0.004/0.01
Predicted hospital mortality % (SAPS II)	32±32	36±28	21±20	39±18	$<10^{-4}$

[a] According to Knaus definitions

Table 7 Late-onset pneumonia in the four different ICU populations

ICUs, centers	I	II	III	IV	*p*
Late-onset pneumonia, *n* (%)	45 (19)	22 (9)	11 (12)	11 (6)	0.0003
Days in ICU when pneumonia developed (mean ± SD)	13±10	9±2	12±17	14±9	0.5
High-risk germs[a], *n* (%)	22 (49)	11 (50)	3 (27)	7 (64)	0.1
Initial appropriate antibiotic coverage[b]	19 (42)	9 (41)	4 (36)	2 (18)	0.26
24 h appropriate antibiotic coverage[b]	30 (67)	17 (77)	6 (55)	7 (64)	0.9
Late-onset pneumonia occurrence					0.08[c]
Hazard ratio[d]	2.95	1.07	1.86	0.149	
95% Confidence interval	1.7–5.2	0.39–2.9	0.65–5.3	0.02–1.2	
p value	2.10^{-4}	0.89	0.24	0.07	

[a] Oxacillin-resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa* or *Acinetobacter* species

[b] Appropriate antibiotic treatment was considered when at least one effective drug was included in the antibiotic treatment. Values are reported as *n* (%)

[c] The Gail and Simon test was used to evaluate the interaction between hazard ratio of mortality associated with nosocomial pneumonia and center

[d] Adjusted for the pre-selected covariates (see Table 6)

model, LOP not immediately adequately treated remained significantly associated with an increased risk of mortality (HR=1.69, 95% CI 1.08–2.65, p=0.022), whereas LOP immediately adequately treated did not (HR=1.44, 95% CI 0.75–2.76, p=0.27].

Late-onset pneumonia according to intensive care unit

Differences in baseline characteristics and crude outcomes between the four ICU populations are shown in Table 6. Incidence of LOP (p=0.0003) and mortality rate (p=0.003) among the different ICU populations were statistically different (Tables 6 and 7). The adequacy of the initial empiric antibiotic therapy was not different among centers. Among the different centers, antibiotic therapy was appropriate in 55–77% of the episodes in the first 24 h. The LOP occurrence was not always associated with increased mortality among the different ICUs. The HRs, even adjusted over the selected prognostic parameters, were different among the ICUs, ranging from 0.149 (95% CI 0.02–1.2) to 2.95 (95% CI 1.7–5.2) (Table 7). However, the center effect did not reach statistical significance (p=0.08, Gail and Simon test).

Discussion

While most clinicians believe that nosocomial pneumonia is responsible for a high mortality, considerable controversy remains in the literature regarding both the incidence and the effect upon prognosis of nosocomial pneumonia in the ICU setting. Our large prospective multicenter study was designed to evaluate attributable mortality associated with LOP after careful adjustment for the severity at admission, the evolution of severity during the first 4 days of ICU stay and the appropriateness of initial empiric antibiotic treatment. We found that pneumonia on ICU admission and a median LOD score greater than 4 at D2 post-ICU admission were associated with an increased risk of the occurrence of late-onset nosocomial pneumonia. Moreover, the severity assessed by SAPS II at admission, as well as the evolution of severity within the first 4 calendar days in ICU, were associated with an increased risk of death in the ICU. After adjustment for these selected prognostic parameters – i.e. McCabe score more than 1, SAPS II and increases in SAPS II within the first 4 calendar days post-admission in ICU – LOP occurrence was associated with a 1.58-fold increased risk of death in patients hospitalized in ICUs. Nevertheless, when appropriateness of initial empiric antibiotic treatment was introduced into the Cox model, inappropriately treated LOP remained significantly associated with an increased risk of death in patients hospitalized in ICUs, whereas appropriately treated LOP did not.

In previous studies targeting the issue of mortality [2, 4, 22, 23, 24, 25, 26, 27], confounders and secondary exposures as factors influencing the outcome of ICU patients with or without nosocomial pneumonia – i.e. daily assessment of severity, length of stay before infection and other nosocomial infections – were not totally excluded. Since severity of illness assessed by SAPS II or APACHE II is considered to be one of the main prognostic factors in ICU patients, most of those studies have only used severity of illness at admission to the ICU to adjust and pair controls to cases. Very few studies have looked at trends in severity in the first few days in the ICU as a prognostic factor and tried to adjust for this very important confounding factor. In a recent study, Soufir et al. [28] showed, in a case control study, that adjusting for severity at 3 or 7 days before the onset of a nosocomial bacteremia dramatically decreased the attributable mortality of this event when compared to the one found when adjusting only for admission severity. In our study, we made particular efforts to adjust the estimation for the initial prognostic factors but also for the evolution of the risk during ICU stay. Dynamic risk factors

were assessed, especially daily assessment of severity, using either general severity indices or organ dysfunction scoring systems, within the first 4 calendar days in ICU. We found that severity indices measured on admission, such as SAPS II, and daily increase of this illness severity score within the first 4 days post-admission were associated with an increased risk of death in ICUs. Furthermore, even after adjustment for these selected prognostic parameters, LOP was associated with an increased risk of death.

The reality of an attributable mortality due to nosocomial pneumonia is still debated [2, 4, 22, 23, 24, 25, 26, 27]. The occurrence of nosocomial pneumonia was shown to achieve a 1.8- to 4-fold increase in the risk of death [2, 4, 22, 24]. However, these results differ from those of Papazian and co-workers [25], Bregeon and colleagues [27] and Baker and colleagues [26]. In these three studies, survival was similar among patients with pneumonia and controls. Differences across these different studies may be partly explained by differences in patients, methods and diagnostic strategies. Criteria used to define pneumonia were not standardized and this could account for a large degree of variability in the reported estimates of pneumonia incidence, mortality and increased length of hospital stay in the literature.

In our study, the manner of diagnosing nosocomial pneumonia was prospectively standardized among the centers. This study used stringent objective diagnostic criteria for the diagnosis of pneumonia. However, the incidence rates of LOP were higher in centers with increased mortality induced by LOP (centers I and III in Table 5). These results could be explained by differences among the various teams in their manner of suspecting pneumonia. One might conclude that LOP was under-diagnosed in some centers, leading to an underestimation of the risk of death associated with LOP. The accuracy of chest X-ray in diagnosing new pulmonary infiltrate is known to be low [29, 30]. Similarly, clinical findings do not improve the low diagnostic accuracy [30]. However, we carefully designed this study to standardize our routine practice. We discussed the results with all the investigators to find any differences in the manner of diagnosing pneumonia and this hypothesis seems unlikely. Unfortunately, audits were not performed in the ICUs to confirm this hypothesis.

The diagnostic accuracy of the bacteriological sample procedures might have influenced the results. Centers I and II preferentially used fibroscopically directed samples and centers III and IV preferentially used blind plugged telescoping catheters. In all centers, a specimen that yielded 10^3 cfu/ml or more was required to make the diagnosis. However, the difference in the diagnostic accuracy of these techniques appeared too smooth to explain the difference observed [31, 32, 33]. Moreover, centers using the same quantitative culture techniques have totally different incidence rates and risks of mortality induced by LOP.

In our study, the increase in mortality associated with LOP varies among centers. The HRs of LOP for inducing death, even adjusted over the selected prognostic parameters, were between 0.149 and 2.95. However, this observable center effect did not reach statistical significance. These discrepant results could not clearly be explained by various baseline characteristics being significantly different among the centers (Table 6). For example, Heyland et al. have recently shown that the attributable increase in mortality was largely seen in medical patients, with essentially no effect seen in surgical patients [23]. The two centers in our study that showed the highest HRs of death (2.95 in center I and 1.86 in center III) enrolled 65% and 35% surgical patients, respectively, compared to 14% and 28% surgical patients enrolled in the centers with either no effect (center II: HR: 1.07) or even 'protective effect' (center IV, HR: 0.15) of LOP on mortality. Furthermore, neither the high-risk germ – i.e. *Pseudomonas aeruginosa*, *Acinetobacter* species and *Staphylococcus aureus* – incidence [4, 5, 6, 34] nor an initial inappropriate empiric antibiotic treatment [23, 35, 36, 37] could explain these differences among the centers. The discrepancies of the results among centers strongly argue for the stratification of the statistical analyses in further multicenter studies in this field.

The main finding of our study is the major effect of an inappropriate initial empiric antibiotic treatment on LOP mortality. After adjustment for the selected prognostic parameters – i.e. McCabe score more than 1, SAPS II and increases in SAPS II within the first 4 calendar days post-admission to ICU – LOP occurrence was significantly and independently associated with an increased risk of death in patients hospitalized in ICUs. Nevertheless, when the initial empiric antibiotic treatment was appropriate, the occurrence of LOP was no longer significantly associated with an increased risk of death, whereas inappropriately treated LOP was. These results are in accordance with previous reports [35, 38, 39]. In studies specially devoted to attributable nosocomial pneumonia mortality [2, 4, 22, 23, 24, 25, 26, 27], the appropriateness of initial antimicrobial therapy as such was rarely mentioned. In other studies providing this information, the percentage of patients who received inappropriate initial antibiotic therapy varies greatly, from 10% to 73% [23, 28, 35, 37, 38, 39, 39, 40, 41]. These differences in initial antibiotic therapy appropriateness could partly explain the controversy concerning the reality of an attributable mortality due to nosocomial pneumonia [2, 4, 22, 23, 24, 25, 26, 27].

Finally, many studies looking at the outcome of nosocomial pneumonia or, more specifically, at the attributable mortality of this disease have been performed. Nevertheless, the increased mortality induced by nosocomial pneumonia in ventilated patients remains a controversial

issue in the literature. In our multicenter study, the main interesting finding is that the mortality attributable to LOP, after adjusting for baseline factors – i.e. initial prognostic factors, but also severity of illness in the first 4 days of ICU stay – is dependent on the appropriateness of the initial empiric antibiotic treatment. These results might justify clinicians considering the early use of broad-spectrum antibiotic therapy in their patients with suspected LOP.

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ANNEXE 6

COLONIZATION WITH METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* IN ICU PATIENTS: MORBIDITY, MORTALITY, AND GLYCOPEPTIDE USE

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ABSTRACT

OBJECTIVE: To determine the impact of methicillin-resistant *Staphylococcus aureus* (MRSA) colonization on the occurrence of *S aureus* infections (methicillin-resistant and methicillin-susceptible), the use of glycopeptides, and outcome among intensive care unit (ICU) patients.

DESIGN: Prospective observational cohort survey.

SETTING: A medical-surgical ICU with 10 single-bed rooms in a 468-bed, tertiary-care, university-affiliated hospital.

PATIENTS: A total of 1,044 ICU patients were followed for the detection of MRSA colonization from July 1, 1995, to July, 1 1998.

METHODS: MRSA colonization was detected using nasal samples in all patients plus wound samples in surgical patients within 48 hours of admission or within the first 48 hours of ICU stay and weekly thereafter. MRSA infections were defined using Centers for Disease Control and Prevention standard definitions, except for ventilator-associated pneumonia and catheter-related infections, which were defined by quantitative distal culture samples.

RESULTS: One thousand forty-four patients (70% medical patients) were included in the analysis. Mean age was 61 ± 18 years; mean Simplified Acute Physiologic Score (SAPS) II was 36.4 ± 20; and median ICU stay was 4 (range, 1-195) days. Two hundred thirty-one patients (22%) died in the ICU. Fifty-four patients (5.1%) were colonized with MRSA on admission, and 52 (4.9%) of 1,044 acquired MRSA colonization in the ICU. Thirty-five patients developed a total of 42 *S aureus* infections (32 MRSA, 10 methicillin-susceptible). After factors associated with the development of an *S aureus* infection were adjusted for in a multivariate Cox model (SAPS II >36; hazard ratio [HR], 1.64; *P*=.09; male gender: HR, 2.2; *P*=.05), MRSA colonization increased the risk of *S aureus* infection (HR, 3.84; *P*=.0003). MRSA colonization did not influence ICU mortality (HR, 1.01; *P*=.94). Glycopeptides were used in 11.4% of the patients (119/1,044) for a median duration of 5 days. For patients with no colonization, MRSA colonization on admission, and ICU-acquired MRSA colonization, respectively, glycopeptide use per 1,000 hospital days was 37.7, 225.2, and 118.5 days. MRSA colonization per se increased by 2.3-fold the use of glycopeptides in MRSA-colonized patients, even when an MRSA infection was not demonstrated, compared to non-colonized patients.

CONCLUSIONS: In our unit, MRSA colonization greatly increased the risk of *S aureus* infection and of glycopeptide use in colonized and non-colonized patients, without influencing ICU mortality. MRSA colonization influenced glycopeptide use even if an MRSA infection was not demonstrated; thus, an MRSA control program is warranted to decrease vancomycin use and to limit glycopeptide resistance in gram-positive cocci (*Infect Control Hosp Epidemiol* 2001;22:687-692).

Methicillin-resistant *Staphylococcus aureus* (MRSA) has emerged as a cause of endemic nosocomial infections throughout the world. Among the consequences of extensive glycopeptide use, vancomycin-resistant enterococci species[1] and, more recently, glycopeptide-intermediate *S aureus*[2-5] are harbingers of a major therapeutic problem for the third millennium, rendering interventions to eliminate MRSA, or at least to limit the spread of MRSA, more important than ever. The results of the European Prevalence of Infection in Intensive Care (EPIC)[6] study reported that the highest prevalence of MRSA strains was found in Italy (81%) and France (78.6%). Moreover, MRSA strains were endemic in several health centers: burn units, dialysis centers, long-term–care facilities, and intensive care units (ICUs). The epidemiology of staphylococcal colonization in ICU patients and its clinical consequences are still poorly understood, because few detailed epidemiological studies have been carried out in this setting. In particular, the effect of MRSA colonization on patient mortality is largely unknown.

In our hospital, where MRSA has been endemic for many years, we evaluated the consequences of MRSA colonization in a large cohort of critically ill patients to assess the relation between MRSA colonization and the occurrence of *S aureus* nosocomial infections, to examine the influence of MRSA colonization on mortality, and to evaluate the impact of MRSA colonization on glycopeptide use.

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METHODS

Study Population

This prospective study was conducted in a medical-surgical ICU having 10 single-bed rooms at the Fondation Hôpital Saint Joseph (Paris, France), a 460-bed, adult, tertiary-care, university-affiliated hospital. From July 1, 1995 to July 1, 1998, all consecutive patients who were admitted in the ICU were enrolled in the study and evaluated for MRSA colonization. Only the first ICU admission during the same hospital stay was included in the analysis.

For each patient, we extracted from the ICU database the following parameters: age, gender, severity of illness on admission using the Simplified Acute Physiologic Score (SAPS) II,[7] need for mechanical ventilation during the first 24 hours, reason for ICU admission, transfer from wards, duration of ICU stay, and ICU mortality.

A computerized pharmacy database was used to determine the patient's daily use of glycopeptides during ICU stay. The reason for glycopeptide use was reviewed retrospectively by one of the investigators (HK).

As this study was only epidemiological and no invasive measures were required to study patients, the Institutional Review Board of Fondation Hôpital Saint Joseph waived the need for informed consent.

Microbiological Surveillance

The detection of MRSA colonization was assessed on nasal samples collected on the admission day or within the first 48 hours of ICU stay, and every Tuesday until MRSA was detected. Samples of wounds in surgical patients also were assessed. Samples were obtained using premoistened cotton-tipped swabs.

MRSA were detected by their ability to grow on Chapman agar containing 4 mg/L of oxacillin after incubation for 24 hours at 37°C. As a presumptive test, Pastorex Staph-plus (Sanofi Diagnostics Pasteur SA, Marnes-La Coquette, France) was used. Isolates were confirmed for identification as *S aureus* by their ability to ferment mannitol and a positive reaction to coagulase.

Definitions of Colonization and Infection

Colonization was considered if one nasal sample was positive for MRSA. Colonization was reported as ICU-acquired only if there was no history of prior MRSA colonization or infection and no positive sample had been detected on admission, plus at least one surveillance sample yielding MRSA after 48 hours of hospitalization. Colonization on admission included patients known to have been colonized outside of the ICU.

S aureus nosocomial infections were infections occurring at least 48 hours after ICU admission, without incubation on admission. Ventilator-associated pneumonia was defined by a new and persistent infiltrate on chest radiograph and a positive quantitative culture of a distal sampling from either a broncho-alveolar lavage (10^4 colony-forming units [CFUs]/mL)[8] or a plugged telescopic-brush catheter (10^3 CFUs/mL).[9] A diagnosis of catheter-related infection was established if there were general signs of infection together with culture of the catheter tip yielding at least 10^3 CFUs/mL.[10] The other types of MRSA infections were defined according to Centers for Disease Control and Prevention (CDC) standard definitions.[11]

Infection Control Program

From the time of the study until the present, the following infection control program to limit the spread of MRSA has been used in the unit: screening of all admitted patients for MRSA; isolation of all patients until they are proven not to be colonized; identification of MRSA patients by adding a flag in their chart; and reinforced barrier precautions with gloves and gowns for all contacts. Hand washing with a 10% povidone-iodine antiseptic preparation is performed before and after each patient contact. Nasal decontamination with mupirocin was not used.

The antibiotic choice for infections depended on clinical conditions, microbiological results, and the physician's discretion. However, to regulate the use of glycopeptides, we instituted a policy that required completion of a glycopeptide continuation form to continue the drug after 72 hours. Subsequent therapy was based on culture-documented resistant organism or, in case of negative cultures, reevaluation and approval by the senior physicians of the unit.

Statistical Analysis

Bivariate analyses used the Mann-Whitney or Fisher's Exact Test for uncensored data and the log-rank test for censored data. Comparison between the consumption of glycopeptides per 1,000 days during non-colonized, colonized, and infected periods was performed assuming a Poisson distribution within each of the groups. All of the variables tested were introduced under their native coding into the multivariate models except age and SAPS II, which were categorized according to the median value observed in the entire sample.

Risk factors for MRSA carriage at admission. An unconditional logistic regression analysis was performed with variables recorded on ICU admission with a P value of $\leq .2$, as assessed by univariate analysis, to control for all confounding factors. Variables were introduced into the logistic regression in a backward manner to construct the final model; the significance level for staying in the model was 0.1.

Risk factors for ICU death. The main endpoint was overall survival from the ICU. Patients who were discharged alive from the ICU were censored at the time of their discharge. The Kaplan-Meier estimate of survival was computed. We first studied the prognostic value for death of several baseline characteristics (age, SAPS II, gender, transfer from ward, tracheal intubation, reason for ICU admission). The search for prognostic factors was based on the log-rank test, which compares the distribution of survival times in several subsets. Variables found to be associated with the outcome (ie, influencing the survival time) by the log-rank test at the 5% level were then entered into a Cox model. Thus, variables that did not add any information to the remainders were not kept in the model. A backward procedure allowed us to select sequentially the variables that

were significantly related to outcome, as tested by the likelihood ratio test at the 10% level. Hazard ratios (HRs) were computed (with 95% confidence intervals [CI_{95}]) and were used to measure relative risk. As a second step, MRSA acquisition was introduced in the final model. The risk of death (ie, the probability that an individual [i] died at a time [t], conditional on his having survived to that time) on p explanatory covariates, Zi(t), was expressed through the Cox model as follows:

$$\propto i(t.Zi)=\propto 0(t)\exp(\beta 1tZ1[t]+\beta 2tZi2[t]+.....+\beta ntZin[t]),$$

where the p covariates appearing in the model with a corresponding βp coefficient either were assessed at baseline (Zi(t)=Zi), such as SAPS II or intubation, or were time-dependent (eg, the acquisition of MRSA). The time-dependent variables took the "0" value before MRSA acquisition and took the "1" value between the time of MRSA acquisition and the time of ICU discharge.

Risk factors for* S aureus *infection. The time to acquisition of the first MRSA infection was computed. The statistical procedure used was similar to that used for computing ICU death.

Statistical analyses were performed using BMDP (BMDP, Los Angeles, CA). Levels of significance were represented by *P* values derived from two-sided tests. Unless indicated, a *P* value of ≤.05 was considered to indicate statistical significance.

RESULTS

Colonization

From July 1, 1995 to July 1, 1998, 1,044 patients were admitted to the ICU and constituted the study group. The 1,044 patients had a mean age of 61±18 years and 741 (71%) of them were medical patients. The mean SAPS II score was 36.4±20. We obtained a total of 2,104 surveillance samples (mean, 2.01 per patient; median, 1; range, 1-28). One hundred forty-eight samples (7%) were positive from the nasal site. The median ICU stay was 4 (range, 1-193) days. Of the 1,044 patients, 106 (10.1%) had MRSA colonization. Of the 106 MRSA cases, 54 (5.1%) were imported and 52 (4.9%) were ICU-acquired, with a ratio of acquired to imported of 0.96. The Figure displays the proportion of ICU patients remaining free from MRSA colonization, by duration of ICU stay. The Table shows the demographics and clinical characteristics of the colonized and non-colonized patients. In a stepwise logistic regression that included age, severity on admission (using the SAPS II score), need of endotracheal tube before admission, the medical status of the patient, and having been transferred from a ward, only two factors remained independently associated with MRSA colonization on admission: transfer from wards (odds ratio [OR], 2.79; CI_{95}, 1.4-5.58; *P*=.002) and intubation at admission (OR , 2.89; CI_{95}, 1.51-5.53; *P*=.004).

Risk Factors for S aureus *Infection*

A total of 42 *S aureus* infections occurred in 35 patients: 32 were MRSA and 10 were methicillin-sensitive *S aureus* ([MSSA] ventilator-associated pneumonias, 6; catheter-related infections, 4). MRSA infections included 14 ventilator-associated pneumonias, 10 catheter-related infections or primary bacteremias, 4 urinary infections, 3 wound infections, and 1 sinusitis. Among these 35 patients, 29 (83%) were colonized with MRSA. Seven patients were colonized and infected on the same day. For the remaining, the median time between the detection of colonization and the diagnosis of *S aureus* infection was 12.5 (range, 1-66) days.

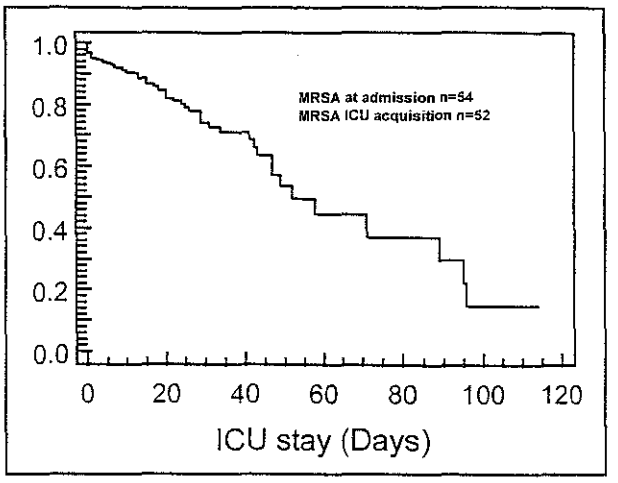

FIGURE. Kaplan-Meier estimates of patients free from methicillin-resistant *Staphylococcus aureus* (MRSA) colonization during their intensive care unit (ICU) stay.

In univariate analysis, patients with *S aureus* infections were more often male (28/35 vs 605/1,009; *P*=.02) and transferred from a hospital ward (24/35 vs 504/1,009; *P*=.036). They were more severely ill on ICU admission (SAPS II score, 43.5 vs 36.2; *P*=.04) and more frequently intubated (35/35 vs 544/1,009; *P*<.001). *S aureus* infections occurred more frequently in patients colonized with MRSA on admission (7/35 vs 46/1,009; *P*<.001).

When the first episode of infection was taken into account, only three variables were independently associated with the occurrence of *S aureus* infections: SAPS II score >36 (HR, 1.64; CI_{95}, 0.8-3.39; *P*=.09), male gender (HR, 2.23; CI_{95}, 1-4.95; *P*=.05), and colonization with MRSA (HR, 3.84; CI_{95}, 1.80-8.08; *P*=.0003).

Risk Factors for ICU Mortality

The crude ICU mortality was 231 (22%) of 1,044. Crude ICU death was higher in colonized compared to non-colonized patients (37.7% vs 20.4%; *P*=.0001; Table) and in infected compared to non-infected patients (15/35 vs 221/1,009; *P*=.003). Eight variables were significantly associated with ICU mortality in univariate analysis (age, male gender, transfer from wards, SAPS II score, OMEGA score, intubation before ICU admission and during the first 24 hours of ICU stay, reason for admission, and MRSA colonization on admission) and were considered for inclusion in the multivariate model. Only two factors were retained in the multivariate analysis as independently associated with

TABLE
DEMOGRAPHIC AND CLINICAL DATA FOR METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* COLONIZED AND NON-COLONIZED PATIENTS

Variable	Colonized	Non-Colonized	*P*
Number	106	938	
Age, y	65.3±12.8	60.6±18.7	.01
Gender (male:female)	72:34	563:374	.14
SAPS II (±SD)	41.10±15.4	35.9±20.5	.01
Mechanical ventilation, no. (%)	96 (90.5%)	482 (51.4%)	.0001
Reason for ICU admission, no. (%)*			
Medical	58 (54.7%)	689 (73.3%)	.0001
Scheduled surgery	11 (11.3%)	91 (9.7%)	
Unscheduled surgery	37 (35.6%)	158 (16.8%)	
OMEGA†	533.4±539	98.3±162	.0001
Transfer from wards, no. (%)	75 (70.7%)	448 (47.7%)	.0001
Length of stay, d (±SD)	33.8±34.8	7.3±10.2	.0001
ICU mortality, no. (%)	40 (37.7%)	192 (20.4%)	.0001

Abbreviations: ICU, intensive care unit; SAPS II, Simplified Acute Physiologic Score; SD, standard deviation.
* Patients were classified as having a surgical admission when they were operated on within 1 week before or after ICU admission and as having a medical admission otherwise.
† The intensity of care was determined by the French OMEGA score. This score describes 47 diagnostic and therapeutic items, weighted from 1 to 20 points, according to the resources used and ranged into three categories. The OMEGA 1 reported 25 items, recorded only once during a stay even though they had been performed several times (such as use of a central line or vasoactive drugs). The OMEGA 2 reported 11 items recorded every time they were performed (such as dialysis or endoscopic or radiographic procedures). The OMEGA 3 reported 8 items recorded every day (such as mechanical ventilation or continuous monitoring). The total OMEGA score is obtained by adding all OMEGA points.

ICU mortality: SAPS II >36 (HR, 4.26; CI_{95}, 2.85-6.36; $P<.0001$) and intubation during the first 24 hours of ICU stay (HR, 3.67; CI_{95}, 2.01-6.68; $P<.0001$). MRSA colonization did not influence mortality (HR, 1.01; CI_{95}, 0.71-1.44; $P=.94$) when it was forced into the Cox model at the last step.

Use of Glycopeptides

Of the 1,044 patients, 119 (11.4%) received a glycopeptide, mainly vancomycin, for a median duration of 5 (range, 1-47) days, with a median daily dose of 1 g. Of the 32 MRSA infections, 30 (94%) were treated with a glycopeptide. The non-colonized patients received glycopeptides for 37.7 days per 1,000 hospital-days, mainly for empirical use (46), prophylaxis (5), and infections (coagulase-negative staphylococci, 8; enterococci, 2). Among the 46 uses of empirical treatment, glycopeptide was stopped in 48 hours in 27 patients after negative cultures and continued in the 19 remaining cases for more than 48 hours, with no documented infection.

The 54 patients colonized with MRSA on admission received 235.2 days of glycopeptide per 1,000 hospital-days. Glycopeptides were used for MRSA infections in 11 patients and empirically in 16 others; 13 patients received empirical glycopeptides for more than 48 hours.

The 52 patients with ICU-acquired colonization received 118.3 days of glycopeptide per 1,000 hospital-days. The reasons for glycopeptide use were as follows: MRSA infections, 19; empirical treatment, 18; prophylaxis, 1; and selective digestive decontamination, 1. Fourteen (78%) of 18 instances of empirical glycopeptide use were for less than 48 hours.

The number of days of glycopeptide use per 1,000 hospitalization days was influenced by MRSA infections (139.2 before vs 522.4 after MRSA infections in patients colonized with MRSA on admission, and 29.3 before vs 246.5 after MRSA infections in patients with ICU-acquired MRSA colonization). Interestingly, MRSA status alone increased by more than threefold the use of glycopeptides in colonized, non-infected MRSA patients compared to non-colonized patients (117.1 vs 35.6 days/1,000 hospital-days, $P<.0001$).

DISCUSSION

Our study was undertaken to examine, in a large cohort of ICU patients, the effects of MRSA colonization on the occurrence of *S aureus* infections, the use of glycopeptides, and outcome. We found that MRSA colonization was a risk factor for the development of *S aureus* infection, suggesting (as have others[13]) that cases of MRSA do not replace, but rather add, to the cases due to MSSA. MRSA colonization increased greatly the use of glycopeptides in colonized and non-colonized patients. The crude ICU mortality of MRSA-colonized patients was higher than that of non-colonized patients. However, MRSA acquisition during ICU stay was not an independent risk factor for ICU death.

Our study showed that 10% of ICU patients had MRSA colonization, with a ratio of acquired to imported cases of 0.96. Our incidence of MRSA colonization was in line with a recent report in ICU patients in the same area in France.[14] To define the high-risk population having MRSA colonization on admission better, we analyzed the characteristics of these patients in a multivariable model. We found that MRSA colonization was recovered more often in patients referred from wards (OR, 2.79) and in patients intubated before ICU admission (OR, 2.89). Further study is needed to develop and vali-

date a score allowing us to discriminate patients at risk for MRSA colonization on admission.

Previous studies have reported that higher severity of illness on admission was a predisposing factor for the acquisition of nosocomial infections.[14,15] Higher severity of illness on admission and MRSA colonization were found to be independent risk factors for the occurrence of *S aureus* (either MSSA or MRSA) infections. Eighty-three percent of the infected patients were previously or simultaneously colonized with MRSA. Several studies found nasal *S aureus* carriage to be a risk factor for acquiring *S aureus* infections in medical[16-18] and surgical[19-22] patients. High-level nasal carriage of *S aureus* was found to be an independent risk factor for developing surgical-site infections with *S aureus*.[21] It is unlikely that the propensity of MRSA to favor *S aureus* infections is higher than that of MSSA. The specific role of MRSA in favoring *S aureus* infections in the ICU probably is due to the high number of patients who received antimicrobials in the ICU. Most of the antibacterials used are active against MSSA strains and might prevent MSSA infections.[15] In 1998, for 52% of the patient–ICU-days, the patients received at least one antimicrobial active against MSSA (co-amoxiclav, tazobactam, third-generation cephalosporins, imipenem, fluoroquinolones, or oxacillin). Our database did not provide individual information about the use of these antimicrobials, and further study is needed to confirm this hypothesis.

The crude mortality in our ICU cohort was 22%; mortality rates among the patients with colonization and infection were 38% and 43%, respectively. Factors independently associated with ICU mortality were those previously reported in ICU patients: severity of illness on admission and need for mechanical ventilation.[23] The relation between MRSA colonization and mortality deserves further comment. Although the crude ICU mortality of MRSA-colonized patients was significantly higher than for non-colonized patients (38% vs 20%), we found that acquisition of MRSA did not influence mortality in ICU patients, even in the presence of an infection. This result might be because patients free of MRSA infections could have another nosocomial infection or other dynamic events occurring during ICU stay that could influence outcome.[24] Our study assessed only the consequences of MRSA colonization and infection.

Few studies have analyzed separately the colonized (non-infected) and infected patients with MRSA as a factor for ICU mortality. In a study by Girou et al[24] that differentiated carriage (one MRSA-positive nasal or cutaneous sample), colonization (one MRSA-positive clinical sample without signs of infection), and MRSA infection, the mortality (33% vs 38% in our study) among carrier patients was significantly less than the mortality in MRSA-colonized or MRSA-infected patients (45% vs 57%, respectively). In a small population of burn patients, a case-control study did not demonstrate a difference in mortality between colonized and infected patients with MRSA.[25]

Vancomycin use was largely dependent on whether or not MRSA was endemic in the unit.[26] The concern that glycopeptide use should be a public health priority has intensified since the first report of glycopeptide-intermediate *S aureus* being isolated in 1996.[27] Moreover, vancomycin use was demonstrated as a risk factor for acquiring vancomycin-resistant enterococci.[28] In 1995, the Hospital Infection Control Practices Advisory Committee recommendations for the control of vancomycin-resistant enterococci emphasized vancomycin restriction as crucial to prevent the spread of vancomycin resistance.[29] Several methods have been proposed to restrict vancomycin use, such as a vancomycin continuation form,[30] stop orders, and educational interventions,[31-33] but the effects of these appeared to be transient.[33] Our study showed that MRSA carriage influenced glycopeptide use in both non-colonized and colonized patients, even when an infection was not demonstrated. This suggests that the best approach to limit the spread of glycopeptide resistance will be concomitant measures to decrease MRSA colonization pressure, inappropriate vancomycin use, and perhaps control of broad-spectrum antimicrobial use as suggested by Monnet et al.[34] MRSA control programs in hospitals have been more often discussed than implemented, despite recent studies showing the benefits of reducing MRSA carriage.[35] A recent cost-benefit analysis demonstrated that a MRSA control program was beneficial compared to no isolation when MRSA colonization on admission ranged from 1% to 7%.[36] An antibiotic-control program could be another important measure to limit MRSA spread. A recent study[37] failed to demonstrate that prior total antimicrobial use was a risk factor for MRSA colonization, but prior fluoroquinolone use was identified as a risk factor for the acquisition of MRSA colonization.[38]

In conclusion, our study demonstrated that MRSA colonization increased the risk of methicillin-resistant and methicillin-susceptible *S aureus* infections without influencing ICU mortality. MRSA colonization influenced glycopeptide use, in both non-colonized and colonized non-infected MRSA patients. Accordingly, strict measures to limit MRSA colonization should be the cornerstone of infection control programs to regulate glycopeptide use.

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ANNEXE 7

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Impact of Unplanned Extubation and Reintubation after Weaning on Nosocomial Pneumonia Risk in the Intensive Care Unit

A Prospective Multicenter Study

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Background: **The authors prospectively evaluated the occurrence and outcomes of unplanned extubations (self-extubation and accidental extubation) and reintubation after weaning, and examined the hypothesis that these events may differ regarding their influence on the risk of nosocomial pneumonia.**

Methods: **Data were taken from a prospective, 2-yr database including 750 mechanically ventilated patients from six intensive care units.**

Results: **One hundred five patients (14%) experienced at least one episode of these 3 events; 51 self-extubations occurred in 38 patients, 24 accidental extubations in 22 patients, and 56 reintubations after weaning in 45 patients. The incidence density of these 3 events was 16.4 per 1,000 mechanical ventilation days. Reintubation within 48 h was needed consistently after accidental extubation but was unnecessary in 37% of self-extubated patients. Unplanned extubation and reintubation after weaning were associated with longer total mechanical ventilation (17 vs. 6 days; $P < 0.0001$), intensive care unit stay (22 *vs.* 9 days; $P < 0.0001$), and hospital stay (34 *vs.* 18 days; $P < 0.0001$) than in control group, but did not influence intensive care unit or hospital mortality. The incidence of nosocomial pneumonia was significantly higher in patients with unplanned extubation or reintubation after weaning (27.6% *vs.* 13.8%; $P = 0.002$). In a Cox model adjusting on severity at admission, unplanned extubation and reintubation after weaning increased the risk of nosocomial pneumonia (relative risk, 1.80; 95% confidence interval, 1.15–2.80; $P = 0.009$). This risk increase was entirely ascribable to accidental extubation (relative risk, 5.3; 95% confidence interval, 2.8–9.9; $P < 0.001$).**

Conclusion: **Accidental extubation but not self-extubation or reintubation after weaning increased the risk of nosocomial pneumonia. These 3 events may deserve evaluation as an indicator for quality-of-care studies.**

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MECHANICAL ventilation *via* tracheal intubation is widely used in intensive care units (ICUs). Reported complications of mechanical ventilation include nosocomial pneumonia, volutrauma, and barotrauma. Complications related to the endotracheal tube itself[1] consist chiefly of reintubation after weaning and unplanned extubation by the patient (self-extubation) or caregivers (accidental extubation). Unplanned extubation is the most common endotracheal tube accident,[1] accounting for about 10% (3–16%) of extubations and require reintubation in 60% of cases.[2–5] Predisposing factors and prevention have been extensively studied.[3,4,6] Despite the development of predictive indices for weaning or extubation, planned extubation fails in 2–19% of cases.[7–14] In a recent case-control study investigating the impact of unplanned extubation on the outcome of patients receiving mechanical ventilation, Epstein *et al.*[15] found that either form of unplanned extubation was associated with longer times on mechanical ventilation and in the ICU and hospital but not with increased mortality.

Reintubation has been recognized as a leading risk factor for nosocomial pneumonia.[16] The risk of nosocomial pneumonia after reintubation may be associated with factors related to the reintubation procedure itself or to factors related to the previous extubation event. Both the rate of reintubation and the circumstances of prior extubation vary across these three categories. No prospective studies specifically designed to evaluate the impact of each of these categories on the occurrence of nosocomial pneumonia have been published. We conducted a prospective multicenter study to evaluate the impact of reintubation after weaning, of self-extubation, and of accidental extubation on the risk of nosocomial pneumonia.

Patients and Methods

Eligibility Criteria

A prospective study in a multicenter database (OUTCOMEREA®) was conducted during a 2-yr period in six French medical or surgical ICUs. Starting in January 1997, all patients who were older than 16 yr, had an ICU stay length longer than 48 h, and received mechanical ventilation at any time during the ICU stay were entered

in the study. Patients who were tracheostomized at ICU admission were excluded from the analyses.

Definitions and Measurements

Method of Data Collection. Data were collected daily by senior physicians in each participating unit. For each patient, an investigator used these data to complete a case report form. All codes and definitions were established prior to study initiation. Before entry into the database, each case report form was reviewed by a member of the steering committee.

Collected Variables. The case report forms contained no information identifying the patient. They were used to record age, sex, and admission category (medical, scheduled surgery, or unscheduled surgery); underlying diseases according to SAPS II definitions[17]; other comorbidities including respiratory, cardiovascular, hepatic, renal, and immunosuppression using APACHE II definitions[18]; and severity of illness at ICU admission and daily during the ICU stay as measured using the SAPS II and LOD system.[19]

All patients were screened daily throughout the ICU stay for suspected nosocomial pneumonia and for self-extubation, accidental extubation, or reintubation after weaning. Self-extubation was defined as deliberate extubation by a patient for whom the intensivists considered that intubation was beneficial, accidental extubation as inadvertent extubation by an ICU caregiver during procedures at the bedside, and reintubation after weaning as a need for reintubation within 48 h after planned extubation. The need for noninvasive mechanical ventilation alone was not considered as an extubation failure.

The sedative regimen used in the overwhelming majority of patients included a combination of a benzodiazepine and an opioid. The level of sedation was routinely titrated to achieve a Ramsay score of 2–3 and was tailored to the needs of each patient depending on the presenting condition.[20,21] In patients with clinical improvement in the initial cause of their respiratory failure, four widely accepted criteria for a trial of extubation were evaluated daily: a ratio of the partial pressure of arterial oxygen over the fraction of inspired oxygen above 200, a positive end-expiratory pressure below 5 cm H_2O, adequate coughing during suctioning, and absence of infusion of sedatives with a Glasgow coma score greater than 14.[22] In addition, in the overwhelming majority of patients subjected to a trial of extubation, the ratio of respiratory frequency over tidal volume was equal to or lower than 105 breaths per minute per liter.[23] Planned extubation was performed only after a successful T-tube trial of 20–30 min.

The sedated Glasgow coma score was defined as the value truly observed, including effect of sedation, and the expected Glasgow coma score was defined as the value of the score expected if the patient was not receiving sedative drugs.

Clinical suspicion of nosocomial pneumonia was based on the criteria described by Andrews *et al.*[24] Nosocomial pneumonia was defined as pneumonia occurring after at least 48 h of mechanical ventilation, according to the recommendations of the First International Consensus Conference on the Clinical Investigation of Ventilator-Associated Pneumonia.[25] The diagnosis of nosocomial pneumonia was based on a chest radiograph showing new pulmonary infiltrates not otherwise explained, positive results of quantitative cultures of a plugged telescopic catheter or protected-specimen brush specimen ($> 10^3$ cfu/ml) or of a bronchoalveolar lavage specimen ($> 10^4$ cfu/ml), and at least two of the following criteria: fever greater than 38°C, purulent bronchial secretions, or peripheral leukocyte count greater than 10,000/mm^3.

Finally, length of mechanical ventilation, length of ICU and hospital stays, and outcomes at ICU and hospital discharges were recorded.

Statistical Analysis

Results were expressed as numerical values and percentages for categorical variables, and as medians and quartiles (25th–75th percentile) for continuous variables. Comparisons were based on the Fisher exact test or chi-square test for categorical data and on paired Wilcoxon tests or Kruskal-Wallis tests for continuous data where appropriate. The relation between iatrogenic events and nosocomial pneumonia was computed using a Cox model with a time-dependent covariate. Time to nosocomial pneumonia was defined as the interval from mechanical ventilation initiation to the first nosocomial pneumonia episode even if nosocomial pneumonia occurred after successful extubation. In patients who had nosocomial pneumonia episodes before and after unplanned extubation and reintubation after weaning ($n = 5$), this time was defined as the interval between mechanical ventilation initiation and the nosocomial pneumonia episode after event. Nosocomial pneumonia episodes that occurred before unplanned extubation or reintubation after weaning were entered into the model as a dichotomous variable. Patients who had no nosocomial pneumonia episodes were censored at ICU discharge. Time to the first self-extubation, accidental extubation, or reintubation after weaning, and time to the first nosocomial pneumonia episode were computed using Kaplan-Meier estimates.

Time to occurrence of the first event (unplanned extubation or reintubation after weaning) and each category of event were successively introduced into the Cox model as time-dependent covariates. In addition, the following variables were studied: SAPS II and LOD on the first mechanical ventilation day, occurrence of pneumonia before mechanical ventilation or within 48 h after mechanical ventilation, enteral feeding, antiacid and antibiotic therapy within 48 h after mechanical ventilation, Knaus comorbidities, main reasons for ICU admission,

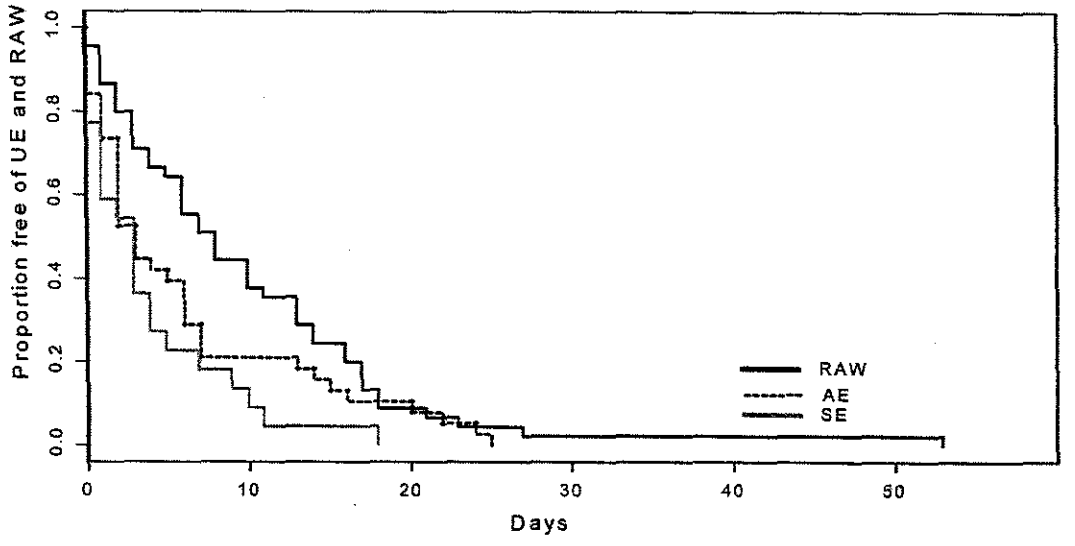

Fig. 1. Time to the first event. RAW = reintubation after weaning; UE = unplanned extubation; AE = accidental extubation; SE = self-extubation.

and whether the patient was transferred to the ICU from a ward. These variables have been reported to affect the risk of mechanical ventilation–related pneumonia.[26] A stepwise forward procedure was used to select variables for entry into the model. Results at the last step are reported.

Factors associated with hospital mortality were evaluated using a Cox model in which unplanned extubation or reintubation after weaning were entered as a time-dependent covariate in addition to the following patient characteristics at ICU admission: SAPS II and LOD, Knaus comorbidities, reasons for ICU admission, and whether the patient was transferred from a ward. Stepwise forward selection was used. At the last step, unplanned extubation and reintubation after weaning were forced into the model to allow an estimation of its effects adjusted on patient characteristics.

All statistical tests were two-tailed, and P values less than 5% were considered significant. Statistical tests were performed using the SAS 8.00 (SAS Inc., Cary, NC) and S-plus 2000 (MathSoft Inc., Seattle, WA) software packages for personal computers.

Results

During the 2-yr study period, 1,227 patients were admitted for longer than 48 h to the participating ICUs. During their ICU stay, 750 patients required conventional mechanical ventilation for more than 24 h, including 567 (75.6%) who were ventilated on ICU admission. The median duration of ventilation was 7 days (25th–75th percentile: 3–14 days). Overall, 7,953 patient-ventilation days were investigated, excluding days of ventilation through a tracheostomy and days of noninvasive ventilation.

Of the 750 ventilated patients, 105 (14.0%) experienced 131 events, with 51 self-extubations, 24 accidental extubations, and 56 reintubations after weaning, yielding incidence density rates of 6.4, 3.0, and 7.0 per 1,000 intubation days, respectively. Twenty-three patients experienced more than one category of event. The first event was self-extubation in 38 patients, with a median time to occurrence since mechanical ventilation initiation of 3 days (25th–75th percentile: 2–6); accidental extubation in 22 patients, with a median time of 3 days (25th–75th percentile: 1–4); and reintubation after weaning in 45 patients, with a median time of 8 days (25th–75th percentile: 6–11) (fig. 1).

The 105 patients with unplanned extubation or reintubation after weaning and the 645 patients without unplanned extubation or reintubation after weaning (controls) differed regarding the main causes of ICU admission and the presence of three comorbidities, namely, respiratory, cardiovascular, and immunosuppression (table 1). The SAPS II and LOD scores on the day before events were significantly higher in the accidental extubation group, whereas the Po_2/Fio_2 ratio and the sedated Glasgow coma score were significantly lower (table 2).

When we recorded the maximum daily SAPS II and LOD score values during the 2 days preceding and the 3 days following the event, we found a significant increase in these values only in the reintubation after weaning subgroup, in which the maximum daily scores were significantly higher after the event than on the day before the event ($P < 0.01$ and $P = 0.03$ for the SAPS II and LOD, respectively).

Five patients with unplanned extubation or reintubation after weaning (3 planned extubation failure and 2

Table 1. Population Characteristics on ICU Admission

Median (25th–75th Percentile) [n (%)]	MV Population (n = 750)	Control (n = 645)	RAW + UE (n = 105)	*P* Value
Age	67 (54–75)	67 (53–75)	70 (56–76)	0.21
Sex (male)	478 (63.7)	408 (63.3)	70 (66.7)	0.7
Main reason for admission				0.01
Coma	137 (18.3)	113 (17.5)	24 (22.9)	
Acute respiratory failure	226 (30.1)	189 (29.3)	37 (35.2)	
Shock	173 (23.1)	154 (23.9)	19 (18.1)	
MOF	48 (6.4)	42 (6.5)	6 (5.7)	
Trauma	11 (1.5)	10 (1.5)	1 (1.0)	
COPD	52 (6.9)	39 (6.0)	13 (12.4)	
Other	103 (13.7)	98 (15.2)	5 (4.8)	
Admission category				0.55
Medical	464 (61.9)	394 (61.1)	70 (66.7)	
Scheduled surgery	97 (12.9)	85 (13.2)	12 (11.4)	
Unscheduled surgery	189 (25.2)	166 (25.7)	23 (21.9)	
Chronic disease				
None	406 (54.1)	356 (54.9)	50 (49.0)	
Respiratory	146 (19.5)	118 (18.3)	28 (26.7)	0.04
Cardiovascular	87 (11.6)	65 (10.1)	22 (21.0)	0.001
Hepatic	52 (6.9)	49 (7.6)	3 (2.9)	0.08
Renal	11 (1.5)	10 (1.5)	1 (1.0)	0.63
Immunosuppression	107 (14.3)	99 (15.3)	8 (7.6)	0.04
SAPS II	47 (35–58)	46 (35–58)	49 (37–58)	0.26
MV on admission	567 (75.6)	484 (75.0)	83 (79.0)	0.37

ICU = intensive care unit; MV = mechanical ventilation; RAW = reintubation after weaning; UE = unplanned extubation; MOF = multiple organ failure; COPD = chronic obstructive pulmonary disease; SAPS = Simplified Acute Physiologic Score.

self-extubations) were treated with noninvasive mechanical ventilation.

Complications of Undesirable Extubation

Reintubation within 48 h after the event was required in all accidental extubations but in only 24 of 38 (63.2%) self-extubations. Among the 91 patients who underwent reintubation, including reintubation after weaning, six (5.7%) were tracheostomized within 48 h after event (reintubation after weaning: 1; accidental extubation: 1; and self-extubation: 4).

Among the 750 patients, 125 (16.7%) acquired 163 episodes of nosocomial pneumonia (table 3). The crude incidence of nosocomial pneumonia was significantly higher in the patients with unplanned extubation or reintubation after weaning (36 of 105; 34.3%) than in the controls (89 of 645; 13.8%) ($P < 0.01$). This significant difference persisted after exclusion of nosocomial pneumonia episodes that preceded the first event (29 of 105; 27.6%; $P = 0.0003$).

Nosocomial pneumonia after event was significantly more common in the accidental extubation subgroup (11 of 22; 50%) than in the reintubation after weaning subgroup (11 of 45; 24.4%) and self-extubation subgroup (7 of 38, 18.4%) ($P = 0.02$). When introduced in a Cox model as a time-dependent covariate, unplanned extubation and reintubation after weaning increased the risk of nosocomial pneumonia (relative risk, 1.80; 95% confidence interval, 1.15–2.80; $P = 0.009$) even after adjustment on SAPS II and LOD on the first mechanical ventilation day, enteral feeding, gastric protection by antihistamine type 2 receptors and proton pump inhibitors, and antimicrobial therapy within 48 h after mechanical ventilation initiation (table 4, which shows only significant variables).

When we studied these three categories of events separately, we found that the increase in nosocomial pneumonia risk associated with unplanned extubation and reintubation after weaning was entirely attributable

Table 2. Severity and Underlying Conditions 24 h before the First Event

Events	RAW + UE (n = 105)	RAW (n = 45)	AE (n = 22)	SE (n = 38)	*P* Value
SAPS II	39 (32–48)	39 (31–49)	48 (38–57)	38 (32–44)	0.027
LOD score	4 (2–6)	4 (2–6)	7 (5–7)	4 (2–6)	0.008
Expected Glasgow Coma Score	15 (13–15)	15 (14–15)	14 (6–15)	14 (12–15)	0.04
Sedated Glasgow Coma Score	13 (7–15)	15 (13–15)	6 (3–13)	12 (7–15)	$< 10^{-3}$
Pao_2/Fio_2 ratio	273 (212–363)	314 (247–367)	228 (192–316)	278 (222–360)	0.05
Oral intubation	95 (90.5)	43 (95.6)	18 (81.8)	34 (89.5)	0.16

RAW = reintubation after weaning; UE = unplanned extubation; AE = accidental extubation; SE = self-extubation; SAPS = Simplified Acute Physiologic Score; LOD = logistic organ dysfunction; Pao_2 = arterial oxygen tension; Fio_2 = fraction of inspired oxygen.

Table 3. Risk Factors for Nosocomial Pneumonia Occurring after the Beginning of Mechanical Ventilation

Variables	RR	95% CI	*P* Value	RR	95% CI	*P* Value
All events (RAW + UE)	1.80	1.15–2.80	0.009			
AE				5.28	2.83–9.89	$< 10^{-3}$
SAPS II at MV	0.99	0.98–1.00	0.044	0.99	0.97–1.00	0.03
Enteral feeding at MV	1.77	1.23–2.53	0.002	1.85	1.30–2.65	0.0007

RR = risk ratio; CI = confidence interval; RAW = reintubation after weaning; UE = unplanned extubation; AE = accidental extubation; SAPS = Simplified Acute Physiologic Score; MV = mechanical ventilation.

to an association with accidental extubation (relative risk, 5.28; 95% confidence interval, 2.83–9.89; $P < 0.01$; table 3). Conversely, no associations with nosocomial pneumonia were found for reintubation after self-extubation (relative risk, 1.83; 95% confidence interval, 0.85–3.96; $P = 0.12$) or reintubation after weaning (relative risk, 1.35; 95% confidence interval, 0.7–2.61; $P = 0.36$). Figure 2 shows that accidental extubations are at earlier risk of nosocomial pneumonia and that the proportion of patients with nosocomial pneumonia is higher with accidental extubations.

Hospital Outcomes of Undesirable Extubation

Total mechanical ventilation duration was significantly longer in the unplanned extubation and reintubation after weaning groups (median, 17 days; 25th–75th percentile: 8–24) than in the control group (median, 6 days; 25th–75th percentile: 3–12) ($P < 0.01$). Significant differences in the same direction were found for ICU and hospital length of stay (table 4). Moreover, mechanical ventilation duration was significantly higher in the subgroup with reintubation after weaning than in the other two subgroups. Tracheostomy was performed in a larger proportion of patients with unplanned extubation or reintubation after weaning (22.9%; reintubation after weaning: 13; accidental extubation: 5; and self-extubation: 6) than of controls (6.0%; n = 39) ($P < 0.01$). The overall additional mechanical ventilation durations after the first event were 11 days (range, 7–16 days), 7 days (range, 5–13 days), and 4 days (range, 1–13 days) for reintubation after weaning, accidental extubation, and self-extubation, respectively.

Unplanned extubation or reintubation after weaning did not influence ICU or hospital mortality rates (table 4), even after adjustment on SAPS II at ICU admission, comorbidities, and reasons for ICU admission.

Discussion

Self-extubation, accidental extubation, and reintubation after weaning are common in the ICU. These three categories of events put patients at significant risk of morbidity and can contribute to death.[5] Although unplanned extubation or reintubation after weaning have been extensively investigated since 1990, most studies focused on incidence, risk factors, prevention, and prediction of early reintubation. Data on adverse events, including nosocomial pneumonia, are sparse. Adverse event rates after unplanned extubation have ranged from 5% to 28%,[27] and life-threatening complications have been reported. All studies of the outcome of unplanned extubation used a retrospective case-control design.[7,8,15,16] We report the first large, prospective, multicenter study evaluating the occurrence and outcomes of all three categories of events, with the primary objective of looking for nosocomial pneumonia rate differences possibly related to differences in reintubation rates or to differences in the circumstances surrounding extubation.

Table 4. Duration of Mechanical Ventilation, Length of Stay, and Mortality Rate among 750 Mechanically Ventilated Patients

Median (Q1–Q2) [n (%)]	All (n = 750)	Control Group (n = 645)	RAW + UE (n = 105)	*P* Value	RAW (n = 45)	AE (n = 22)	SE (n = 38)	*P* Value
Ventilation								
Duration of MV	7 (3–14)	6 (3–12)	17 (8–24)	< 0.001	21 (14–28)	12 (7–19)	13 (5–21)	0.005
Cumulated MV days	7,953	6,020	1,933		1,021	345	567	
Duration of MV before event	—	—	5 (3–12)		9 (4–15)	4 (2–6)	4 (2–8)	
Duration of MV after event	—	—	8 (4–15)		11 (7–16)	7 (5–13)	4 (1–13)	
Mortality								
ICU mortality rate	276 (36.8)	245 (38.0)	31 (29.5)	0.10	14 (31.1)	9 (40.9)	8 (21.1)	0.25
Hospital mortality rate	329 (43.9)	286 (44.3)	43 (41.0)	0.52	20 (44.4)	12 (54.5)	11 (29.0)	0.12
LOS								
ICU LOS (days)	10 (6–20)	9 (5–17)	22 (11–40)	< 0.001	27 (18–43)	19 (9–35)	18 (10–36)	0.04
ICU LOS before event	—	—	6 (3–14)		9 (4–16)	4 (4–6)	6 (3–8)	
ICU LOS after event	—	—	15 (8–27)		16 (10–29)	11 (7–34)	14 (6–24)	
Hospital LOS (days)	21 (10–37)	18 (9–33)	34 (22–54)	< 0.001	38 (25–68)	31 (16–45)	30 (18–49)	0.11

RAW = reintubation after weaning; UE = unplanned extubation; AE = accidental extubation; SE = self-extubation; MV = mechanical ventilation; ICU = intensive care unit; LOS = length of stay.

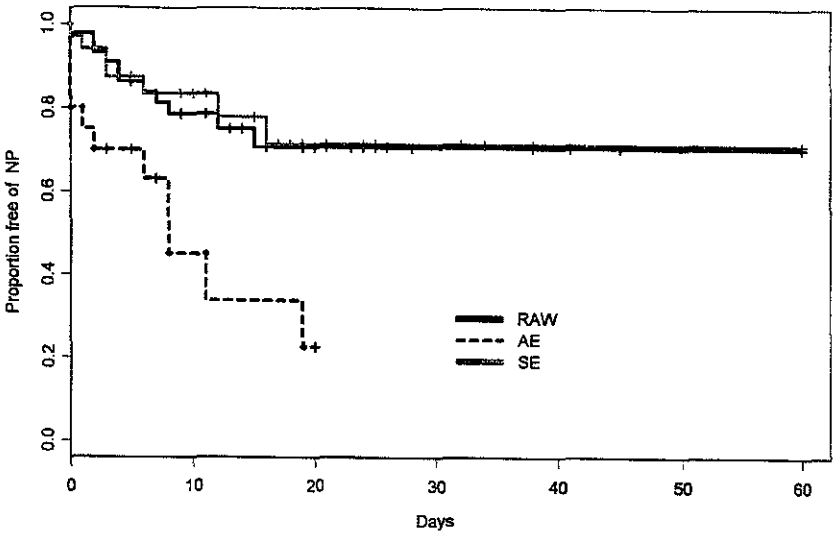

Fig. 2. Time to occurrence of the first nosocomial pneumonia episode in each of the three categories (time to first nosocomial pneumonia was computed from day of event to nosocomial pneumonia occurring after event). NP = nosocomial pneumonia; RAW = reintubation after weaning; AE = accidental extubation; SE = self-extubation.

The limitations of this study need to be discussed. First, the use of continuous intravenous sedation is associated with the prolongation of mechanical ventilation and a greater incidence of reintubation, and could be a risk factor for nosocomial pneumonia.[28] We did not use daily interruption of sedative drug infusion as suggested by Kress *et al.*,[29] since the results of their study had not been published at the time the data on our patients were collected. Sedative drug interruption may influence the rate of unplanned extubation. Second, the ICU patients in the present study were all hospitalized for longer than 48 h. Consequently, the self-extubation subgroup was not representative of the overall population with this event, which often occurs shortly after ICU admission of suicidal or postsurgical patients. This probably led us to underestimate the proportion of self-extubated patients who did not require reintubation. Third, among patients with unplanned extubation, those with accidental extubation were significantly more likely to require reintubation than those with self-extubation.[4] The rate of accidental extubation was higher in our unplanned extubation group (37%) than in other series (0–22%).[2–6,15,27,30] This explains why the overall reintubation rate among patients with unplanned extubation (77%) was at the upper end of the range reported in the literature (30–88%).[2–4,6,15,27,30,31] Fourth, the Consensus Conference criteria from 1993 that we used for diagnosis of ventilatory associated pneumonia could be viewed as out-of-date. However, all patients were similarly screened for diagnosis of nosocomial pneumonia.

In our population, incidence rates were 4.8% for self-extubation and 2.8% for accidental extubation (7.6% for unplanned extubation). These rates are similar to the 3–16% rates of self-extubation found in other studies.[3,4,6,15,30,32–35] Our incidence rate of reintubation after weaning was 6%, which is within the 2–19% range reported in the literature.[7–14,22] This wide range reflects differences in the time to reintubation used to define reintubation after weaning (from within 24 h to within 72 h of planned extubation).

Recent studies have measured the frequency of unplanned extubation as incidence densities. Values ranged from 1.6 to 40 per 1,000 mechanical ventilation days, which is in agreement with our value of 9.4.[1,2,15,31,35–37]

In agreement with most previous studies, we found no increase in mortality in the patients who experienced unplanned extubation or reintubation after weaning, as compared with the controls.[3,15,27,30,33,38,39] The recent literature found that reintubation was associated with an increase in mortality rate.[4,7,11,31] In the present study, the mortality rate was nonsignificantly higher in the patients with accidental extubation or reintubation after weaning, all of whom required reintubation. Several recent series found that mortality was significantly higher in patients with reintubation after weaning,[7,8,10,11] ranging from 32% to 43%, in keeping with our findings; mortality was only 4–12% in successfully extubated patients.[7,8,10,11,16]

Our study hypothesis was that the rate of nosocomial pneumonia would vary across these three categories as a result of differences in reintubation rates or in the circumstances surrounding the previous extubation. Reintubation can introduce colonized oropharyngeal secretions into the lower airways.[40] Torres *et al.*[16] reported that reintubation was among the most significant risk factors for nosocomial pneumonia, with a sixfold risk increase. However, these studies failed to distinguish between the risk of nosocomial pneumonia associated with reintubation *per se* and the risk associated with the circumstances of extubation. Our findings support a role for these circumstances: although we found nosocomial pneumonia rate differences across categories, those differences did not mirror reintubation rates. The reintubation rate was far lower in the self-extubation category, and the rate of nosocomial pneumonia was also lower in these patients. However, all patients with reintubation

after weaning or accidental extubation required reintubation, but nosocomial pneumonia was far more common in the accidental extubation category. Several factors may explain these differences. The pathogenesis of nosocomial pneumonia is related to aspiration of pharyngeal contents or gastric content[41] into the distal airways. Factors that may affect the risk of nosocomial pneumonia after unplanned extubation or reintubation after weaning include altered glottic function after several days of intubation, trauma related to the inflated tube cuff in unplanned extubation, prior level of sedation, level of consciousness after extubation,[42] presence of a nasogastric tube during the extubation period,[43] body position, and time spent extubated.[16] Reintubation after weaning occurred when the patients were awake, whereas in our accidental extubation subgroup alterations in consciousness were present in most patients (median sedated Glasgow coma score, 6) and the median Pao_2/Fio_2 ratio was significantly lower than in the other two groups. Both parameters have been found to be associated with reintubation.[4] Although by definition reintubation is always performed after reintubation after weaning, removal of the tube in this situation is done under optimal conditions, including stomach emptying, previous cessation of enteral feeding, careful airways suctioning, deflation of the tube cuff, and close monitoring. Most studies of nosocomial pneumonia rates in patients with unplanned extubation[7,8,10,11,16] found no significant association[3,5,7,27] but included few[7,27] or no[3,5] patients with accidental extubation. Accidental extubations may occur in sicker patients with heavier workload and therefore more opportunities of manipulations leading to accidental events. However, in the Cox model we used, adjustment on severity and organ failure scores has been performed. Therefore, this study shows clearly that accidental extubation remains an independent predictor of nosocomial pneumonia, adjusted on patients severity.

Total mechanical ventilation duration was significantly longer in our self-extubation, accidental extubation, and reintubation after weaning subgroups than in the controls, and all three events were significantly associated with longer ICU and hospital stays. Moreover, although the self-extubated patients were less likely to undergo reintubation, their mechanical ventilation length, ICU stay length, and hospital stay length were significantly longer than in the controls. In keeping with our findings, Epstein *et al.*[7] reported than mechanical ventilation duration was about 2 weeks longer in patients who underwent reintubation. In contrast, in a case-control study by Chevron and coworkers,[4] total mechanical ventilation length was significantly lower in patients with than without unplanned extubation (9 days and 16 days, respectively). This discrepancy may be ascribable in part to the low reintubation rate (37%) in the study by Chevron *et al.*[4] and in part to exclusion from our study of patients with ICU stays shorter than 48 h. Nevertheless, it has been suggested that unplanned extubation not followed by reintubation indicates that planned extubation was overdue and that this may translate into a higher rate of ventilator-related complications, a longer ICU stay, and higher costs.[34]

Given that unplanned extubation and reintubation after weaning were associated with longer durations of mechanical ventilation and hospital stay, these events are markers for suboptimal quality of care. Both reintubation after weaning (with its risk of health status deterioration) and accidental extubation (with its risk of nosocomial pneumonia) can be reduced by improving the quality of care. Self-extubation is also partly preventable.[1] Initiation of a continuous quality improvement program was followed by a decrease in the self-extubation rate from 2.6% to 1.2% per patient-ventilator day.[36] It has been suggested that unplanned extubation should be viewed as quality-control issues.[44] These events correspond to different facets of suboptimal care. Accidental extubation may be related to less-than-ideal nursing care. In a recent study, accidental extubation was the fourth most common incident observed in ICUs with nurse understaffing.[45] In a study that used the PRN_{REA} score, Chevron *et al.*[4] demonstrated that accidental extubation was not related to the nurse workload, suggesting that this event may be a consequence of faulty nursing care and could be used as an indicator for nursing care quality. Self-extubation without subsequent reintubation may indicate that intubation was maintained too long because the intensivists underestimated the patient's ability to tolerate weaning; reintubation after weaning may reflect overestimation of this ability. Attempts to prevent self-extubation may result either in premature planned extubation responsible for an increase in the rate of reintubation after weaning or in increased use of deep sedation responsible for an increase in mechanical ventilation duration.[46] In both cases, mechanical ventilation duration would be increased. Whether clinical judgment used alone or in combination with mechanical respiratory indices, such as frequency/tidal volume, is effective in predicting successful extubation remains controversial.[10,12–14,23,47] Continuous quality control programs should evaluate clinical procedures, including clinical indicators, predictive weaning indexes based on pulmonary function parameters, and daily routine evaluation of criteria for a trial of extubation, the goal being to extubate patients as soon as possible but not too soon.[13,14,22,29,47] It would be of interest to evaluate both self-extubation and reintubation after weaning as part of a continuous quality improvement program to determine the ratio of self-extubation over reintubation after weaning that minimizes ventilator days, length of stay, and mechanical ventilation–related complications. To be relevant, a quality indicator should be a common event that is associated with morbidity, easy to detect prospectively, and ame-

nable to prevention.[48] Unplanned extubation and reintubation after weaning meet all of these requirements and consequently deserve evaluation as quality indicator for quality improvement programs.

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Appendix

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