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Risk factors of reccurence, relapse and treatment failure of hospital acquired pneumonia in ICU patients

An observational, retrospective, national study

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ABSTRACT

Objective. Hospital-acquired pneumonia (HAP) is one of the most frequent nosocomial infections in intensive care unit, with no clear impact of treatment failure. The objective of our study was to describe the frequency and impact on outcomes of treatment failure, then to identify risks factors independently associated with treatment failure.

Materiel and methods. We conducted a retrospective, observational, national study including two previous cohort : PneumoCare study and Atlanrea cohort. We first analyzed the two cohorts separately. The impact on morbid-mortality of treatment failure was analyzed through univariate analysis. We identified potential risks factors that were included in a multivariate analysis to create a validate score, and we tested these score in the other cohort.

Results. We included 444 patients from the PneumoCare study, including 129 (29.1%) patients with treatment failure, and 624 patients from the Atlanrea cohort, including 155 (24.8%) patients with treatment failure. Treatment failures were associated with increased duration of mechanical ventilation ($p < 0.001$ and $p < 0.05$) and ICU stay ($p < 0.001$ and $p < 0.05$). In a multivariate analysis, treatment failure was independently associated with in-ICU mortality (OR = 2.01, p = 0.001). Risks factors of treatment failures identified were age, monotherapy, infection due to *E. coli*, acute respiratoy distress syndrome and early-onset ventilator associated pneumonia, but no validate bedside score could be created because of poor fitness of fit of the models.

Conclusion. Treatment failure is frequent and is independently associated with an increase of mortality. Risks factors were identified but no strong validate score has been created. Impact of the definition of treatment failure still need to be investigated.

Keywords. Hospital-acquired pneumonia, ventilator-associated pneumonia, risk factors, recurrence, relapse, intensive-care units

RESUME

Objectif. Les pneumonies acquises à l'hôpital font parties des infections nosocomiales les plus fréquentes en réanimation. L'impact d'un échec de traitement n'est pas connu. L'objectif de notre étude est de mettre en évidence la fréquence et l'impact de l'échec de traitement, puis d'identifier des facteurs de risque associés de façon indépendante à l'échec de traitement.

Matériel et méthode. Nous avons conduit une étude rétrospective, observationnelle, nationale en incluant deux cohortes déjà construites : l'étude PneumoCare et la cohorte Atlanréa. L'impact sur la morbi-mortalité a été analysé de façon univariée. Nous avons identifié des facteurs de risque potentiels que nous avons inclus dans une analyse multivariée pour créer un score validé.

Résultats. Nous avons inclus 444 patients de l'étude PneumoCare et 624 de la cohorte Atlanréa, dont 129 (29.1%) et 155 (24.8%) patients avec un échec de traitement. Cet échec était associé à une augmentation de la durée de ventilation mécanique ($p < 0.001$ et $p < 0.05$) et du séjour en réanimation ($p < 0.001$ et $p < 0.05$). En analyse multivariée, il y a une augmentation de la mortalité (OR = 2.01, $p = 0.001$). Les facteurs de risque identifiés sont l'âge, la monothérapie, l'infection à *E. coli*, le syndrome détresse respiratoire aigue et le caractère précoce (< 5 jours) de la pneumonie. Nous n'avons pas pu créer de score valide en raison d'un test de Hosmer-Lemeshow inférieur à 2.2 x 10-16.

Conclusion. L'échec de traitement des pneumonies acquises à l'hôpital est associé à une plus grande morbi-mortalité. Des facteurs de risque ont été identifiés mais aucun score valide n'a pu être créé. L'impact de la définition de l'échec de traitement doit être étudié.

Mots-clés. Pneumonies nosocomiales, pneumonies acquises sous ventilation mécanique, récidive, rechute, facteurs de risque, réanimation.

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TABLE DES MATIERES

1 - INTRODUCTION

Hospital-acquired pneumonia (HAP) is one of the most frequent causes of nosocomial infection in the world (1). In intensive care units (ICU), HAP is the most frequent cause of infection (1–3), with up to 40% of patients ventilated for more than 48 hours developing an episode of HAP (4). HAP, which is the first cause of antibiotic consumption at the hospital (5), is associated with prolonged mechanical ventilation, prolonged duration of ICU stay, and attributable mortality of 13% (6). There is thus a medical need to improve the treatment of this dramatic condition.

European (7) and French (8) guidelines for the treatment of HAP were released in 2017. Even in ICUs with high rates of adherence to recommendations, the rates of HAP remained high, and up to 25% of patients treated for HAP are not cured at the end of treatment (9). Treatment failures have been proposed as an outcome of interest when testing new therapies for HAP, yet there is no consensual definition, and association with clinical outcomes has not been thoroughly investigated (10). Indeed, some patients still present with the clinical presentation of HAP at the end of the 7-8 days of treatment, while others develop a second episode of HAP after few days free of symptoms. Moreover, relapse is considered when a second episode of HAP with at less one common micro-organism with the first episode, while recurrence defined a second episode of HAP with no common pathogen.

We questioned if treatment failure of HAP is associated with an increased risk of mortality and if the definition of treatment failure impacts this association. We aimed to establish the incidence and effect of treatment failures in two large, national patient cohorts. We also identified risk factors of treatment failure of HAP.

2 - METHODS

2.1 Study design

This study is a retrospective analysis of two independent data sets using statistical tools.

2.2 Ethics and committee

The protocol was approved by the Comité d'éthique de la recherche en Anesthésie-Réanimation the 6th april 2020 (CERAR IRB 00010254-2020- 041). No informed consent was needed for this secondary analysis of data sets. The study protocol of the PneumoCare study was approved by the Comité d'éthique de la recherche en Anesthésie-Réanimation (CERAR IRB 00010254-2017-020) (9). Patients and relatives were informed of the trial could refuse the collection of their medical data. Consent was waived according to French law because the trial was a collaborative institutional quality improvement initiative applied to all patients. For the Atlanrea cohort (11), the local ethics committee of the University Hospital of Nantes approved the study protocol (Groupe Nantais d'Ethique dans le Domaine de la Santé, Nantes, France). The need for written consent was waived in this epidemiological study because of its observational design.

2.3 Population

We included all adult patients with one or more episodes of HAP included in the PneumoCare study (9) or the Atlanrea cohort (11). Patients with no data on HAP treatment failure were excluded. Pregnant women and patients under legal guardianship were not included in the original cohorts.

The PneumoCare study was designed to evaluate the effects of implementing the French Guidelines on Hospital-Acquired Pneumonia (9). This nationwide study was conducted in 35

ICUs from 30 hospitals and included 1856 adult patients hospitalized in ICU for three days or more. The Atlanrea study is a cohort of severe trauma and brain-injured (traumatic and non-traumatic) adults requiring invasive mechanical ventilation and hospitalized in 6 surgical ICUs in Western France. An adjudication committee blindly reviewed all the diagnoses of HAP and test-of-cure visits.

2.4 Objectives and endpoints

The primary endpoint was treatment failure, defined as relapse, recurrence, or persistence of initial symptoms at the test of cure.

The secondary objectives were studying the impact on morbidity and mortality of the presence of a treatment failure. The secondary endpoints were the mortality rate in ICU, the length of stay in ICU, the duration of invasive mechanical ventilation.

2.5 Data collection

There was no specific data collection for this study. Data collected for inclusion in the previous cohorts were used. This data concerning admission's reason, medical history, outcomes, mechanical ventilation, the occurrence of hospital-acquired pneumonia, its characteristics, its severity, and its management, prevention of HAP, the severity of the initial disease.

2.6 Definitions

Hospital-acquired pneumonia occurred at least 48 hours after hospital admission and was defined, following French guidelines (8) as 1) radiological signs on chest X-ray: the appearance of a new infiltrate or changes in an existing infiltrate; 2) at least one of the sign between body temperature > 38°C, leucocytosis> 12G/L and leukopenia < 4G/L; 3) and two

signs between the following: purulent pulmonary secretions, increase in oxygen requirement of increase in the level of respiratory support, cough, dyspnea. Ventilator-associated pneumonia (VAP) was defined as pneumonia that occurs after 48 hours of mechanical ventilation. It can occur after extubation or after ICU discharge. The Clinical Pulmonary Infection Score (CPIS) was not used in the two cohorts.

Treatment failure was considered as recurrence, relapse, superinfection, and/or persistence of initial symptoms at the test of cure visit (day 7-10 of treatment). Recurrence was defined as a second episode of HAP with no common micro-organism with the first episode of HAP. Relapse was defined as the second episode of HAP, with one or more common micro-organisms between the two episodes.

2.7 Statistical Analysis

Each cohort was analyzed separately. First, we identified potential risks factors in each cohort with univariate analysis, and all factors with a p-value <0.20 were included in a logistic regression multivariate. Then, we reproduced this statistical model in the other cohort to test reproducibility. If the results were different between the two cohorts, the Atlanrea model was selected due to the homogeneity of the population included in this cohort compared to the PneumoCare cohort.

A simplified score to predict the risk of treatment failure was constructed with variables identified in this statistical model. Sensibility, specificity, negative predictive value, and positive predictive value were tested in the two cohorts.

Receiver operating characteristic (ROC) curves were constructed. The area under the curve (AUC) and its 95% confidence interval evaluated the discrimination of this test, and the Hosmer-Lemeshow test evaluated calibration.

For morbidity and mortality, factors identified in univariate analysis were included in a logistic regression multivariate including the two cohorts.

Continuous variables were expressed in the median (Interquartile Range, IQR) for non-parametric data and mean (Standard Deviation, SD) for parametric data. Quantitative variables were expressed in percentage (%). The level of statistical signification was fixed at $p \leq 0.05$.

Missing data were considered censured and were not simulated.

All analyses were performed with SAS software version 9.4 (SAS Institute Inc, Cary, North Carolina).

3 - RESULTS

3.1 Population and primary endpoint

Out of the 527 patients included in the PneumoCare study who had developed HAP, 444 patients remained in our analysis (83 patients were excluded because there was missing data on HAP evolution), out of which 129 patients (29.1%) had a treatment failure (Figure 1).

Out of the 3500 patients included in the Atlanrea cohort, 624 (17.8%) developed HAP and were kept in our analysis, and 155 (24.8%) had a treatment failure (Figure 1). The characteristics of the two populations are described in Table 1.

3.2 Secondary endpoints

In the PneumoCare study, the rate of in-ICU death was 13.8% in patients with treatment success vs. 27.9% in patients with treatment failure ($p < 0.001$). In the Atlanrea cohort, the rate of in-ICU death was 19.2% in patients with treatment success vs. 20.8 % in patients with

treatment failure (p = 0.68) (Table 2). In a multivariate analysis including (Table 3), treatment failure was associated with an increased risk in mortality (adjusted OR = 2.03 [1.3-3.1] p =0.001), whereas HAP without failure was not associated with increased mortality (p = 0.60).

In the PneumoCare study treatment failures were associated with increased duration of mechanical ventilation (22 *vs* 10 days, p < 0.001) and ICU stay (32 *vs* 18 days, p < 0.001), and increased mortality in ICU (27.91% *vs* 13.83%, p < 0.001) and at day 90 (27.13 % *vs* 13.5%, p = 0.001) (Table 2)

In the Atlanrea cohort, treatment failures were also associated with increased duration of mechanical ventilation (26 *vs* 13 days, p < 0.05) and ICU stay (36.5 *vs* 20 days, p <0.05), but there was no impact on mortality on ICU (20.78% *vs* 19.26%, p = 0.682) or at day 90 (22.14% *vs* 23.1%, p = 0.224) (Table 2).

3.3 Risks factors associated with treatment failure

3.3.1 PneumoCare Study

In the univariate analysis, the factors potentially associated with treatment failure were : age (p = 0.06), severity at ICU admission (p = 0.061 for IGS-II and p = 0.025 for the SOFA score), admission for trauma (p = 0.016), ARDS criteria at the time of HAP diagnosis (p < 0.001), septic shock at the time of HAP diagnosis (p= 0.04), identification of *Escherichia coli* in respiratory fluids (p = 0.004), the absence of bacterial identification (p = 0.023), and the use of monotherapy (p = 0.008) (Table 4). These criteria were thus included in the multivariate analysis, which served to build an easy-to-use score.

The final multivariate analysis selecting the factors independently associated with treatment failure retained: age (OR = 0.98 CI 95% [0.97-0.99], p = 0.006), infection by *Escherichia coli*

(OR = 1.9 CI 95% [1.01-3.7], p = 0.04) and monotherapy (OR = 2.1 CI 95% [1.3-3.5], p = 0.003) (Table 5).

3.3.2 Atlanrea cohort

In the univariate analysis, the factors potentially associated with treatment failure were : age (p = 0.026), sex (p = 0.009), ARDS (p = 0.001), early onset ventilator associated pneumonia (before day 5) (EOVAP) (p = 0.001), hypoxemia (p = 0.021) and lower PaO2/FiO2 ratio (p < 0.05) (Table 4)

The final multivariate analysis selecting the factors independently associated with treatment failure retained: age (OR = 0.98, CI 95% [0.97-0.99], p = 0.03), ARDS (OR = 1.9, CI 95% [1.3-2.8], p = 0.0006, and EOVAP (before day 5) (OR = 1.9, CI 95% [1.3-2.8], p = 0.001) (Table 5)

3.4 A simplified score of HAP treatment failure

We constructed a simplified score including all variables identified in the multivariable analysis from the Pneumocare study (Table 5). The Hosmer-Lemeshow test was inferior to 2.2 $x10^{-16}$. Because of these low calibration tests, no ROC curves were constructed.

We also constructed a simplified score including variables identified in the Atlanrea cohort. The Hosmer-Lemeshow test was inferior to 2.2 x10-16. Thus, we decided not to construct ROC curves.

4 - DISCUSSION

In our study, treatment failure was found in about 25% of our patients and was associated with an increase in the duration of mechanical ventilation, ICU stay, and mortality. Excepted for monotherapy in the PneumoCare study, no modifiable independent risk factor was due to the antimicrobial therapy management. Age, monotherapy, infection due to *E. coli*, hypoxemia, acute respiratory distress syndrome, and early-onset VAP (< 5 days of hospitalization) were associated with treatment failure, but no validation score was developed because of a poor significance.

One of the strengths of this study is that we included a large population from 30 centers. It included patients from different types of ICU and represents the actual practices of treatment of HAP.

Treatment failure was found in 24.8 to 29.1% of patients, depending on the cohort. This rate is concordant with the previous study of Combes (12), which reported a rate of 23%.

There was an increased risk of mortality and an increased duration of mechanical ventilation. Melsen (6) showed in 2013 an increased risk of mortality associated with HAP, which might be due to a prolonged stay in ICU instead of a specific risk ok mortality due to HAP. However, there is an attributable mortality rate of 13% for HAP, and it seems possible that treatment failure of pneumonia will be associated with a higher mortality rate.

There was no impact on mortality in the Atlanrea cohort. This might be because this cohort was in the majority composed of traumatic and non traumatic brain-injured patients. These patients are at high risk of pneumonia (13), but the impact of mortality seems to be lower in this population. A meta-analysis published by Li and al (13) in 2020 shows that VAP does not change the mortality rate in patients suffering from traumatic brain injury (TBI) but increases

the ICU stay and the duration of mechanical ventilation. In 2013, Cinotti and al (14) showed on a single-center, retrospective study that patients suffering from severe subarachnoid hemorrhage were at high risk of early-onset VAP, without any consequences on mortality rate. Robba and al (15) also show in 2020 in a large, prospective, European, observational study that the incidence of VAP in patients suffering from TBI does not affect mortality. This, it is not surprising that treatment failure of HAP does not affect mortality in the Atlanrea cohort.

Patients admitted for traumatic injury were at higher risk of developing HAP and treatment failure of HAP in the PneumoCare cohort. This observation is concordant with literature describing that traumatized patients are at higher risk of developing HAP (3). Since most of the patients included in the Atlanrea cohort suffer from traumatism or non-traumatic injury, it is not surprising that the admission's reason was not associated with treatment failure.

In the PneumoCare cohort, infection due to *Escherichia coli* was associated with a higher risk of treatment failure. Previous studies evaluating the risks factors of treatment failure of pneumonia do not identify this micro-organism as a risk factor. In 2003, Combes (12) show that the microbiological characteristics of the first episode were not associated with a risk of treatment failure, but the rate of infection due to *Escherichia coli* was as low as (4%) compare to our study (from 10 to 20%). A more extensive study shows (10) that non-fermenting gram-negative bacilli and Methicillin-resistant *staphylococcus aureus* were associated with treatment failure. Ranger and al (16) showed in an observational study including 113 patients from a trauma ICU that non-fermenting gram-bacilli was associated with relapse rather than recurrence, probable due to non-response to the initial antimicrobial treatment. Our results are not concordant with these findings. This might be because less than 10% of our patients were infected with these pathogens.

Early onset-HAP was associated with an increased risk of treatment failure in the Atlanrea cohort, but there was no difference in the PneumoCare Study. Since 1992, it is known that patients suffering from traumatic brain injury are highly susceptible to HAP (17). No study had shown an association between early-onset HAP and treatment failure, but some studies tried to prevent EOVAP by administering an antimicrobial treatment early after intubation in these traumatic brain-injured patients. A national, double-blind, randomized, controlled trial including 354 patients evaluates the role of Ceftriaxone to reduce the rate of early onset-VAP (NCT02265406). They will also evaluate the rate of ventilator-associated events, including the number of HAP (18).

ARDS was associated with an increased risk of treatment failure in the univariate analysis and the multivariate analysis of the Atlanrea cohort. This is concordant with the existing literature. Even if Combes (10) did not identify ARDS as a risk factor of treatment failure in the PNEUMO Trial in 2007, he identified in 2003 (12) ARDS as a condition influencing the apparition of the second episode of pneumonia. Siempos (19) also showed in a meta-analysis that ARDS at the time of the initial diagnosis of VAP was associated with treatment failure.

Monotherapy was identified in the PneumoCare study as a risk factor of treatment failure. This is discordant with a recent review. In 2016, Le and al (20) analyzed 3571 patients suffering from HAP. They compared monotherapy versus combination therapy and showed no difference in mortality rate, clinical cure rate, and superinfection rate, but they did not analyze the treatment failure rate. Only four studies evaluated the impact of monotherapy versus combination therapy. Damas (21) showed no impact of monotherapy on treatment failure.

Our study has several limits. First, this is a retrospective study, and the data collected were not the same for the two cohorts. Thereby, we should have missed some risks factors. However,

the data collected corresponds to potential risk factors that could be modified. Even if we may have missed data on the evolution during the first episode, like biological or radiological data, no action can be taken on these potential risk factors. Our study aims to find risks factors on which prevention measures could be applied. Second, they might have some bias. Patients included in the Atlanrea cohorts are not representative of all the patients from ICU, but mostly traumatized and brain-injured patients. Due to neurological conditions, medical withdrawal can affect the impact on mortality. Moreover, they are exposed to more complications, including HAP treatment failure, due to trauma-induced immunosuppression (22), and prolonged ICU length of stays. Third, the cohorts were not designed to evaluate the risk of treatment failure. There might have been some inconsistency in the diagnosis of HAP that was not clearly defined in the Atlanrea cohort. Even if an adjudication committee blindly reviewed all the diagnoses of HAP, there might be some misclassification due to a lack of data. Fourth, there is a lot of missing data concerning the management of antimicrobial treatment of the first episode of HAP. This could have an impact on the rate of second episodes. Fifth, we did not evaluate the impact of the definition of the apparition of a second episode of pneumonia on the outcome. Recurrence and relapse could have different risks factors, as shown by Rangel (16), who studied only risks factors of relapse. Moreover, a relapse could be associated with worse outcomes because of the persistence of the same micro-organism and could be associated with treatment failure. The absence of recovery after ten days could impact the outcome of the patients. The impact of the definition will be tested in further analyses. Finally, we did not validate the score in the external cohort. The scores will be validated in two international cohorts, SMART and ENIRRI.

5 - CONCLUSION

In this retrospective analysis of data sets, treatment failure of hospital-acquired pneumonia was frequent and independently associated with in-ICU mortality. We identified age, acute respiratory distress syndrome, and early-onset VAP as risks factors of treatment failure in patients with HAP, but we cannot develop a predictive score of treatment failure because of a low calibration test. External validation in other cohorts will strengthen our findings.

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7 - APPENDIX

Figure 1. Flow chart HAP = hospital-acquired pneumonia

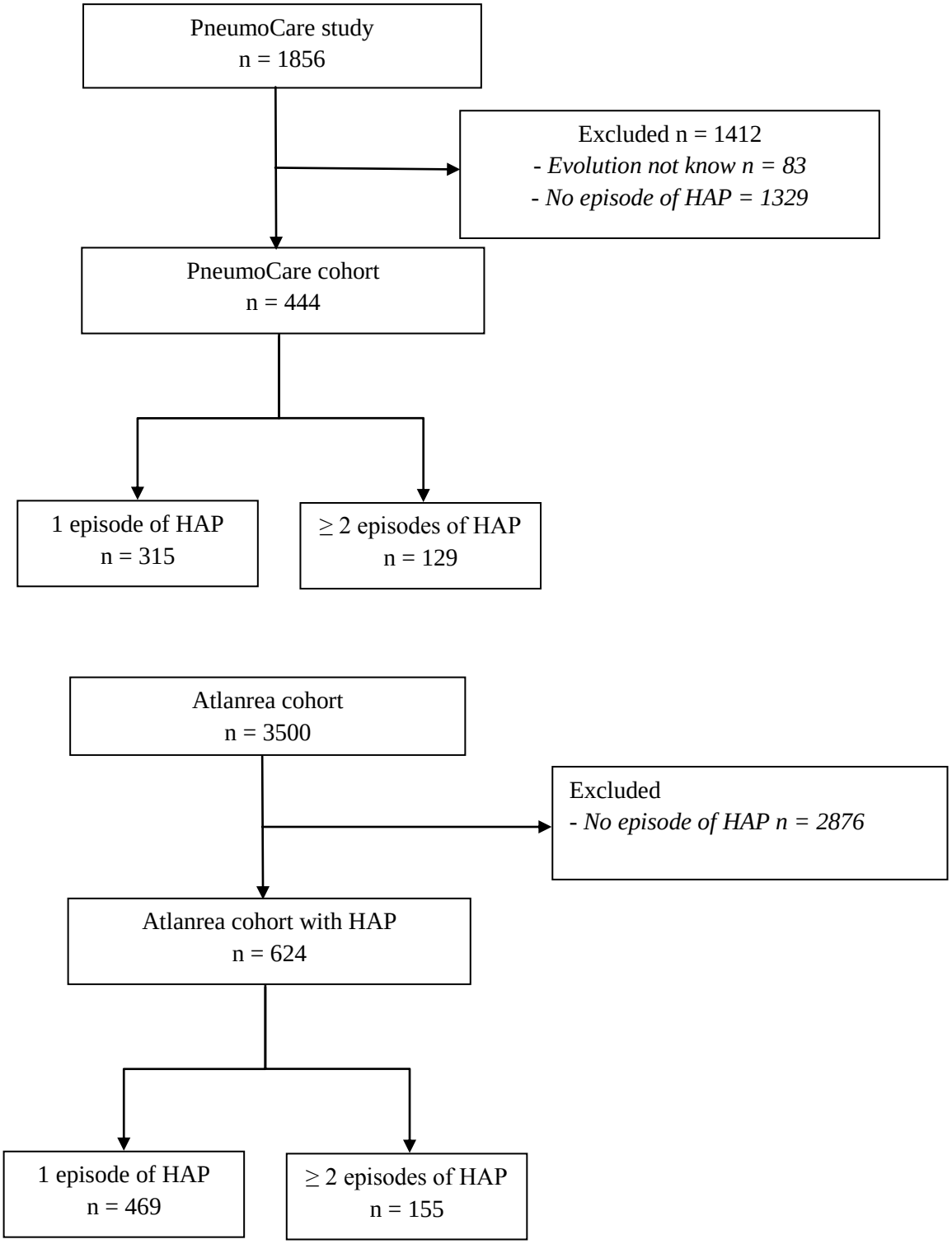

Table 1. Population Characteristics

	Pneumocare study			Atlanreacohort		
	No treatment failure	Treatment failure	p-value	No treatment failure	Treatment failure	p-value
Number of patients	315	129		469	155	
Age, year	61 [48 ; 70]	56 [41 ; 69]	0.06	54 [37 ; 65]	48 [33.5; 61.5]	0.026
Male,	230 (73.0)	100 (77.52)	0.324	318 (68.2)	119 (79.3)	0.009
Cause of admission						
Surgery	145 (46.0)	43 (33.3)	0.016	ND	ND	ND
Medicine	101 (32.06)	43 (33.3)	0.016	ND	ND	ND
Trauma	69 (21.9)	43 (33.3)	0.016	267 (56.93)	93 (60)	0.84
Non-traumatic brain damaged	ND	ND	ND	182 (38.81)	58 (37.42)	0.84
Medical history						
Immunodepression	18 (5.71)	3 (2.33)	0.127	10 (2.15)	5 (3.33)	0.412
Chronic obstructive pulmonary disease	30 (9.58)	11 (8.53)	0.728	19 (4.08)	11 (7.33)	0.126
Bronchiectasis	3 (0.96)	2 (1.55)	0.593	ND	ND	--
Colonization by resistant bacteria	11 (3.51)	1 (0.78)	0.107	ND	ND	--
Foreign hospital stay	2 (0.65)	1 (0.78)	0.875	ND	ND	--
Risk factor of MRSA*	22 (6.98)	10 (7.75)	0.776	ND	ND	--
IGS-II	45 [34; 57]	49 [38; 59]	0.061	46[37 ; 56]	45[36.5;55]	0.31
Sequential Organ Failure Assessment	7 [4; 9]	8 [5; 10]	0.025	8 [6 ; 10]	8 [6 ; 10]	0.432

* Risk factors of MRSA : colonization, chronic skin lesion, chronic dialysis or lCU with MRSA frequency > 10 ;

MRSA = Methicillin-Resistant *Staphylococcus aureus*

Table 2. Association of HAP treatment failure with outcomes

	PneumoCare study			Atlanrea cohort		
	No treatment failure	Treatment failure	p-value	No treatment failure	Treatment failure	p-value
Number of patients	315	129		469	155	
Duration of invasive mechanical ventilation, days	10 [4 ; 18]	22 [16 ; 32]	<0.001	13 [8 ; 22]	26 [19; 38.25]	<0.05
Duration of non-invasive ventilation, days	0 [0 ; 4]	0 [0 ; 1]	0.662	0 [0 ; 1]	0 [0 ; 2]	0.39
Duration of ICU hospitalization	18 [11 ; 28]	32 [23 ; 45]	<0.001	20 [13 ; 29]	36.5 [24 ; 48]	<0.05
In-ICU death	43 (13.83)	36 (27.91)	<0.001	89 (19.26)	32 (20.78)	0.682
28-day death	36 (11.58)	19 (14.73)	0.363	ND	ND	ND
90-day death	42 (13.5)	35 (27.13)	0.001	95 (23.1)	31 (22.14)	0.224

ICU: intensive care unit

Table 3. Multivariate analysis of the risk of death in ICU

	Odds Ratio	CI95	P-value
No pneumonia	Ref	-	-
HAP without treatment failure	1.1	0.6-1.3	0.6
HAP with treatment failure	2.03	1.3-3.1	0.001
IGS II	1.04	1.04-1.05	$<10^{-16}$

ICU = intensive care unit, HAP = Hospital acquired pneumonia, CI = confidence interval

Table 4. Association of the characteristics of HAP with treatment failure

	Pneumocare study			Atlanrea cohort		
	No treatment failure	Treatment failure	p-value	No treatment failure	Treatment failure	p-value
Number of patients	315	129		469	155	
Risk factors of resistant bacteria						
Antibiotherapy within the last 90 days	100 (31.9)	39 (30.47)	0.761	ND	ND	--
Prior antibiotherapy duration (days)	5 [3 ; 7.5]	4.5 [2.2 ; 7.7]	0.666	ND	ND	--
Hospitalisation duration (> day 5)	163 (51.7)	71 (55.04)	0.528	ND	ND	--
Extra-renal epuration	22 (6.98)	11 (8.53)	0.574	ND	ND	--
ARDS	55 (17.46)	44 (34.11)	<0.001	188 (40.3)	87 (56.13)	0.001
Admission for Septic shock	59 (18.91)	28 (21.88)	0.478	ND	ND	--
HAP onset, days	4 [2 ; 7]	4 [3 ; 6.25]	0.449	5 [3 ; 7]	4 [2 ; 5]	<0.05
Late onset VAP (> 5 days)	101 (33.1)	40 (32.26)	0.864	244(52.36)	55 (35.7)	0.001
Max. Body temperature (°C)	38.5 [38 ; 38.9]	38.4 [37.8; 38.9]	0.207	38.5 [38 ; 39]	38.5 [37.8 ; 38.9]	0.308
Leukocytosis > 12 G/L	186 (60.2)	75 (58.59)	0.756	ND	ND	---
Hypoxemia*	235 (76.1)	96 (75)	0.815	299 (63.9)	114 (74.0)	0.021
Lowest PaO2/FiO2	180 [127 ; 232]	150 [112 ; 195]	0.011	165 [121;227.5]	132.5 [95.4;174]	< 0.05
Septic shock at the time of HAP	74 (23.72)	43 (33.33)	0.037	ND	ND	--
Chest imaging	279 (89.1)	121 (93.8)	0.129	469 (100)	155 (100)	
X-ray	270 (96.8)	118 (97.52)	0.688	ND	ND	--
CT-scan	46 (16.73)	18 (15.25)	0.717	ND	ND	--
Imaging findings						
Opacities	234 (84.8)	100 (84.75)	0.993	ND	ND	--
Atelectasis	93 (34.2)	34 (29.06)	0.322	ND	ND	--
Lung abscess	3 (1.1)	2 (1.71)	0.626	ND	ND	--
Pleuresia	45 (16.42)	18 (15.38)	0.798	25 (5.34)	11 (7.1)	0.429

Bacteria involved in HAP				N = 462	N = 153	
Polymorphic flora	38 (12.06)	12 (9.3)	0.403	25 (5.41)	6 (3.92)	0.668
MSSA	80 (25.4)	35 (27.13)	0.705	128 (27.7)	56 (36.6)	0.668
MRSA	4 (1.27)	2 (1.55)	0.816	3 (0.65)	1 (0.65)	0.668
Pseudomonas aeruginosa	22 (6.98)	11 (8.53)	0.574	12 (2.6)	2 (1.31)	0.668
Escherichia coli	35 (11.11)	28 (21.71)	0.004	41 (8.87)	15 (9.8)	0.668
Klebsiella pneumonia	32 (10.16)	7 (5.43)	0.11	25 (5.41)	10 (6.54)	0.668
Haemophilus influenza	51 (16.19)	22 (17.05)	0.824	67 (14.5)	22 (14.38)	0.668
Citrobacter	15 (4.76)	5 (3.88)	0.683	ND	ND	--
Acinetobacter	3 (0.95)	0 (0)	0.266	3 (0.65)	1 (0.65)	0.668
Negative bacterial culture	21 (7.42)	2 (1.67)	0.023	ND	ND	--
Empirical monotherapy	121 (47.3)	67 (62.62)	0.008	ND	ND	--
Total duration of antibiotherapy, days	7 [7 ; 8]	7 [7 ; 10]	0.002	ND	ND	--

* Hypoxemia: need to increase FiO2 > 20% for 4 hours or more.

ARDS: acute respiratory distress syndrome, HAP: hospital-acquired pneumonia, MSSA: methicillin-susceptible Staphylococcus aureus

Table 5. Multivariate analysis of the risk of treatment failure

	PNEUMOCARE model			ATLANREA model		
	Odds Ratio	IC95	P value	Odds Ratio	IC95	P value
Age	0.98	0.97-0.99	0.01	0.98	0.97-0.99	0.03
P/F ratio	0.9	0.9-0.9	0.03	-	-	-
Monotherapy	2.1	1.3-3.5	0.003	NA	NA	NA
E. coli	1.9	1.01-3.7	0.04	-	-	-
ARDS	-	-	-	1.9	1.3-2.8	0.0006
EOVAP	-	-	-	1.9	1.3-2.8	0.001

P/F = PaO2 / FiO2, E. coli = Escherichia coli, ARDS = Acute respiratory distress syndrome, EOVAP = early-onset ventilator associated pneumonia

8 - **ABBREVIATIONS**

ARDS : Acute respiratory distress syndrome

AUC : Area under curve

EOVAP : Early-onset ventilator associated pneumonia

HAP : Hospital-acquired pneumonia

ICU : Intensive Care Unit

IQR : Interquartile range

MSSA: Methicillin-susceptible *Staphylococcus aureus*

MRSA : Methicillin-Resistant *Staphylococcus aureus*

ROC : Receiver operating characteristic

SD : Standard Deviation

TBI : Traumatic brain injury

VAP : Ventilator-associated pneumonia

NOM : POULAIN PRENOM : Cécile

Thesis Title : Risk factors of reccurence, relapse and treatment failure of hospital acquired pneumonia in ICU patients

An observational, retrospective, national study

ABSTRACT

Hospital-acquired pneumonia is one of the most frequent nosocomial infection. This observational, retrospective, national study based on the PneumoCare study and Atlanrea cohort included 1068 patients, including 284 with treatment failure. This treatment failure is associated with an increased intensive-care unit (ICU) stay ($p < 0.001$ and $p < 0.05$) and an increased duration of mechanical ventilation ($p < 0.001$ and $p < 0.05$) and an increased risk of mortality in a multivariate analysis (OR = 2.03, [1.3-3.1] $p < 0.001$). Risks factors highlighted are age, acute respiratory distress syndrome, monotherapy, infection due to *E. coli* and early-onset ventilator associated pneumonia (< 5 days). No score could be constructed, but the impact of the definition of treatment failure has to be evaluated.

MOTS-CLES

Hospital-acquired pneumonia, ventilator-associated pneumonia, risk factors, recurrence, relapse, intensive-care units

NOM : POULAIN PRENOM : Cécile

Titre de Thèse : Facteurs de risque de rechute, récurrence et échec de traitement des pneumonies acquises à l'hôpital chez les patients de réanimation

Etude observationnelle, rétrospective, nationale

RESUME

Les pneumonies acquises à l'hôpital font parties des infections nosocomiales les plus fréquentes. Cette étude observationnelle, rétrospective, nationale basée sur les patients des études PneumoCare et Atlanréa a inclus 1068 patients dont 284 ayant un échec de traitement de pneumonie. Cet échec de traitement est associé à une augmentation de la durée en réanimation ($p < 0.001$ et $p < 0.05$) et de la durée de ventilation mécanique ($p < 0.001$ et $p < 0.05$), et en analyse multivariée à une augmentation de la mortalité (OR = 2.03, [1.3-3.1] $p < 0.001$). Les facteurs de risque mis en évidence sont l'âge, le syndrome de détresse respiratoire aigue, la monothérapie, l'infection à *E. coli* et le caractère précoce de la pneumonie. Aucun score n'a pu être construit mais l'impact de la définition de l'échec de traitement reste à évaluer.

MOTS-CLES

Pneumonies nosocomiales, pneumonies acquises sous ventilation mécanique, récidive, rechute, facteurs de risque, réanimation.

Vu, le Président du Jury,
(tampon et signature)

Professeur David BOUTOILLE

Vu, le Directeur de Thèse,
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Professeur Antoine ROQUILLY

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NOM : POULAIN PRENOM : Cécile

Facteurs de risque de rechute, récurrence et échec de traitement des pneumonies acquises à l'hôpital chez les patients de réanimation

Etude observationnelle, rétrospective, nationale

RESUME

Objectif. Les pneumonies acquises à l'hôpital font parties des infections nosocomiales les plus fréquentes en réanimation. L'impact d'un échec de traitement n'est pas connu. L'objectif de notre étude est de mettre en évidence la fréquence et l'impact de l'échec de traitement, puis d'identifier des facteurs de risque associés de façon indépendante à l'échec de traitement.

Matériel et méthode. Nous avons conduit une étude rétrospective, observationnelle, nationale en incluant deux cohortes déjà construites : l'étude PneumoCare et la cohorte Atlanréa. L'impact sur la morbi-mortalité a été analysé de façon univariée. Nous avons identifié des facteurs de risque potentiels que nous avons inclus dans une analyse multivariée pour créer un score validé.

Résultats. Nous avons inclus 444 patients de l'étude PneumoCare et 624 de la cohorte Atlanréa, dont 129 (29.1%) et 155 (24.8%) patients avec un échec de traitement. Cet échec était associé à une augmentation de la durée de ventilation mécanique ($p < 0.001$ et $p < 0.05$) et du séjour en réanimation ($p < 0.001$ et $p < 0.05$). En analyse multivariée, il y a une augmentation de la mortalité (OR = 2.01, $p = 0.001$). Les facteurs de risque identifiés sont l'âge, la monothérapie, l'infection à *E. coli*, le syndrome détresse respiratoire aigue et le caractère précoce (< 5 jours) de la pneumonie. Nous n'avons pas pu créer de score valide en raison d'un test de Hosmer-Lemeshow inférieur à 2.2 x 10-16.

Conclusion. L'échec de traitement des pneumonies acquises à l'hôpital est associé à une plus grande morbi-mortalité. Des facteurs de risque ont été identifiés mais aucun score valide n'a pu être créé. L'impact de la définition de l'échec de traitement doit être étudié.

MOTS-CLES

Pneumonies nosocomiales, pneumonies acquises sous ventilation mécanique, récidive, rechute, facteurs de risque, réanimation.