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Jules LECOMTE

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Facteurs de risque de résistance bactérienne des pneumonies liées aux soins en post-opératoire de chirurgie cardiaque

Risk factors for bacterial resistance in hospital-acquired pneumonia after major heart surgery

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Président : Monsieur le Professeur Bertrand ROZEC

Directeur de thèse : Docteur Raphaël CINOTTI

Membres du jury :
Pr. David BOUTOILLE,
Pr. Cyril FLAMANT,
Pr. Antoine ROQUILLY

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Abstract :

Background : Pneumonia remains the most frequent infection in the peri-operative period of cardiac surgery and impairs the outcome. Clinicians are challenged in their therapeutic choice between a narrow or a broad-spectrum empirical antibiotic therapy. Our primary objective was to develop and validate a clinical, bed-side compatible, predictive score of bacterial resistance in the context of pneumonia during post-operative period of cardiac surgery. Our secondary objectives were to describe the epidemiology of pneumonia after cardiac surgery, analyse clinical practices and patients' outcomes.

Method : We performed a multicentre retrospective study in three University centres in France. Patients undergoing cardiac surgery with cardiopulmonary bypass were eligible. The diagnosis of pneumonia was performed by the clinician and a quantitative respiratory tract sample was necessary. Two cohorts were created : the "learning cohort" to develop the score and the "validating cohort" to validate its capacities. Univariate analysis was performed to select variables of interest. We then built the predictive model from theses variables with a logistic regression method.

Results : 293 patients were included, 207 in the learning cohort and 82 in the validating cohort. Retained variables for the development of the model were the transfusion count of platelet concentrate ($p=0.051$), antibiotic therapy with carbapenems ($p=0.084$) and a known colonization (cutaneous collection or previous infection) with resistant pathogen. The area under the receiving operator characteristic curve of the predictive model was 0.62 95%CI [0.52 – 0.75]. Patients receiving an inappropriate empirical antibiotic therapy have had more revision surgery ($p=0.03$), longer duration of cardio-pulmonary bypass ($p=0.03$) and clamping time ($p<0.001$). No difference in outcomes was found between appropriate and inappropriate empiric antimicrobial therapy : antibiotic therapy success ten days after pneumonia onset ($p=0.1$), length of stay in the intensive care unit ($p=0.68$) and in the hospital ($p=0.83$), death rate in the ICU ($p=0.54$) and in the hospital ($p=0.63$).

Conclusion : Our model has a low predictive power and is not able to help clinician in the decision between narrow and broad-spectrum antibiotic therapy in the empirical treatment of hospital-acquired pneumonia after major heart surgery.

Abbreviations list :

AIDS : Acquired ImmunoDeficiency Syndrome

AUC : Area Under the Curve

BMI : Body Mass Index

CABG : Coronary Artery Bypass Grafting

CERAR : Comité d'Éthique de la Recherche en Anesthésie-Réanimation

CI : Confidence Interval

COPD : Chronic Obstructive Pulmonary Disease

CPB : Cardio-Pulmonary Bypass

ECLS : ExtraCorporeal Life Support

ESCPM : *Enterobacter c., Serratia m., Citrobacter F., Proteus sp., Morganella m.*

HAP : Hospitalized Acquired Pneumonia

ICU : Intensive Care Unit

IQR : Interquartile Range

LVEF : Left Ventricular Ejection Fraction

MHS : Major Heart Surgery

MRSA : Methicillin resistant *Staphylococcus aureus*

ROC : Receiving Operator Characteristic

SAPS II : Simplified Acute Physiology Score II

SOFA score : Sepsis-related Organ Failure Assessment score

VAP : Ventilator Associated Pneumonia

WHO : World Health Organization

Introduction :

In 2019, the World Health Organization (WHO) reaffirmed the importance of addressing growing antimicrobial resistance and has declared that antimicrobial resistance is one of the top 10 global public health threats facing humanity (1).

Ventilator Associated Pneumonia (VAP) and Hospitalized Acquired Pneumonia (HAP) are frequent complications in post-operative period of cardiac surgery (2). The incidence ranges from 2.1 to 13% of all patients and reaches 35% in patients who are ventilated for more than 48 hours (3). That complication strongly impacts the post-operative recovery period of patients by increasing mortality and length of stay in intensive care unit (ICU) (3,4). Specific risk factors of HAP and VAP after cardiac surgery such as ascending aorta surgery, number of blood units transfused or the need for revision surgery have been identified (5), as well as general risk factors of bacterial resistance in HAP and VAP (6). Nevertheless, to our knowledge, there is no score describing the risk factors for bacterial resistance in the context of HAP after cardiac surgery. In 2017, the European and American guidelines on the management of HAP and VAP stated the interest of defining a population who could receive appropriate narrow-spectrum empiric antibiotic therapy rather than broad-spectrum multidrug therapy (7,8).

The aim of our study was to develop and validate a bedside clinical and biological predictive score to help clinicians to choose between narrow and broad-spectrum antibiotics in the empiric treatment of HAP and VAP after cardiac surgery.

Methods :

Study design

Our study was retrospective between January 2014 and January 2020 in three intensive care units of cardiac surgery, in three University centres in France.

The study protocol has been approved by the French Society in Anaesthesia and Critical Care ethics committee (CERAR – *Comité d'éthique de la Recherche en Anesthésie-Réanimation, Société Française d'Anesthésie-Réanimation*, France, N° IRB 00010254 - 2019 - 045). Because of the retrospective design, no consent was needed.

Inclusion criteria

Adult patients (≥ 18 years), undergoing cardiac or thoracic surgery with cardiopulmonary bypass (CPB) were included. Only the first episode of HAP was selected. A positive quantitative distal respiratory tract sample was required.

Exclusion Criteria

Patients were excluded in case of pregnancy, HAP diagnosis in the first 48h of ICU hospitalization, the lack of antibiotic susceptibility test in respiratory samples.

Pneumonia diagnosis and treatment

In all centres, the diagnosis and treatment were performed during multi-disciplinary staff, in accordance with international recommendations. If more than one HAP or VAP occurred during ICU stay, only the first episode was analysed.

The validity of radiographical and biological diagnosis of pneumonia has been verified retrospectively. According to Leone M et.*al* (6), a valid radiographic and biological diagnosis of HAP was retained if :

Two successive chest radiographs showing new or progressive lung infiltrates in the absence of medical history of underlying heart or lung disease, a single chest radiograph is enough

and at least one of the following signs :

- Body temperature > 38,3 °C without any other cause,

- Leukocytes < 4000/mm^3 or ≥ 12,000/mm^3.

Narrow and broad-spectrum resistance

Narrow-spectrum sensitivity was retained if all bacteria were sensitive to Ampicillin-Sulbactam and third generation cephalosporins (6,9).

Narrow-spectrum resistance was retained if any involved bacteria had a resistance to Ampicillin-Sulbactam or third generation cephalosporins.

Interpretative reading was used to analyse bacterial antibiotics resistance. Indeed, due to a high risk of chromosomal AmpC induction, ESCPM group (*Enterobacter cloacae, Serratia marcescens, Hafnia alvei, Citrobacter Freundii, Morganella morgani, Proteus sp.)* was considered as resistant to narrow-spectrum treatment (10,11).

Inappropriate antimicrobial therapy

The inappropriate therapy was retained if at least one pathogen identified in the respiratory tract sample was resistant to the empiric antibiotic therapy.

Data collection

Demographical, clinical and biological data collected were age, sex, body mass index (BMI), high blood pressure, chronic obstructive pulmonary disease (COPD), diabetes, dialyzed chronic renal

failure, tobacco consumption, hospitalization in past 90 days, transfer from another hospital, known colonisation with resistant pathogen (cutaneous sampling or previous infection), immune deficiency (hemopathy, AIDS, cancer, diabetes, graft), Euroscore II, preoperative hemoglobin, left ventricular ejection fraction, beta-blocker treatment, steroid treatment (> 5mg per day) and myocardial infarction in the past 6 months.

Perioperative collected data were the type of surgery, the duration of surgery, aortic clamping, CPB, circulation arrest, the need for hypothermia during surgery, the amount of blood, platelets and plasma transfusion.

The postoperative data collected were the need for revision surgery, SOFA at ICU admission, SAPS II, the amount of blood, platelets and plasma transfusion, duration and type of antibiotic therapy and/or prophylaxis, pathogens involved, antibiotic susceptibility test, nasal decontamination, days of dialysis, days of cardiac assistance and days of catecholamine usage.

The collected data regarding the outcome were the development of mediastinitis, duration of mechanical ventilation, recovery at day 10 of antibiotic therapy (no need for new antibiotic therapy), length of stay in ICU and in hospital, in-hospital mortality and in-ICU mortality.

All data were collected retrospectively and were gathered during daily care.

Surgery classification

Different types of surgery have been classified using the Euroscore II classification (12) with three additional categories (lighter to heavier surgery) : isolated Coronary Artery Bypass Grafting (CABG), one procedure other than CABG, two procedures, three procedures or more, thoracic aorta surgery, cardiac assist and graft. If the patient matched multiple categories, the procedure with the higher rate of complications was retained.

Primary objective : development of a scoring system

The primary objective was to develop and validate a usable, bed-side compatible, scoring system for the prediction of bacterial resistance. We created two different cohorts of patients. The "Learning cohort" was used to develop the predictive score. The "Validating cohort" was used to validate the score in a similar population.

We dichotomized patients in the validating and learning cohort according to the volume centre : the centre with the highest volume of patients was used for the learning cohort and the other centres for the validating cohort.

Secondary objectives

The secondary objectives were to describe the epidemiology of HAP and VAP after cardiac surgery and to analyse clinical practices and patients' outcomes.

Statistical Analysis

Continuous data are expressed as mean ± standard deviation or median [inter quantile range (IQR)] and compared with the Student t-test. Nominal data are expressed as N(%) and compared with χ^2 or Fisher's exact test whenever appropriate.

The development of the predictive model started with cleaning and correction of outliers if applicable. Missing values were imputed using the MICE method (Multiple Imputation by Chained Equations). Variables with more than 15% missing values were not imputed as this would cause too much uncertainty in the interpretation of the results.

Potential risks factors were identified in the learning cohort by univariate analysis with a p-value cut-off of 0.2. Considering the objective of developing a clinical and bedside compatible score, only relevant and before pneumonia onset criteria were selected for multivariate analysis. In addition, we selected useful variables to the model using the Boruta method.

We have operated a backward selection to obtain the final logistic regression model. The final model is presented with crude odds ratio (OR) and 95% confident interval (95%CI). The discrimination power of the model was evaluated using the area under the ROC curve. Due to a low predictive capacity of the model, the construction of the score was illusive and therefore was not done.

Analyses were performed using software RStudio version 1.4.17.17 (Rstudio, inc. software) and R version 4.1.0 (R foundation for statistical computing) with packages "lubridade", "dplyr" and "ggplots2".

Results :

In the three centres, 956 patients were included, 293 were retained for final analysis, after exclusion of patients with missing data we retained 207 patients in the learning cohort and 82 in the validating cohort. Flowchart is shown in Figure 1.

Demographical and clinical data of learning and validating cohort are shown in Table 1. In the learning cohort the median age was 65 years [56 – 72], 78% of patients were male. The median Euroscore II was 5.9 [2.8 – 13.6], 63% of patients had normal LVEF (≥50%), 16% had mild to moderate dysfunction (LVEF 30-49%), 14% had severe dysfunction (LVEF 20-29%), 6% had extremely severe dysfunction (<20%).

In the learning cohort, most common surgeries were coronary arterial bypass grafting (15%), biological aortic valve replacement (11%) and biological mitral valve replacement (11%).

Different types of surgeries and categories distribution are shown in Table 2.

In the learning and validating cohort, a total of respectively 144 (69%) and 54 (66%) pneumonia were classified as resistant to narrow-spectrum antibiotic therapy. Considering all patients, resistant pathogens were predominantly *Pseudomonas aeruginosa* (21%), *Enterobacter cloacae* (13%), *Hafnia alvei* (10%) and *Serratia marcescens* (10%). In the learning cohort 63 (31%) and in the validating cohort 28 (34%) patients developed a susceptible to narrow-spectrum antibiotic therapy pneumonia. *Escherichia coli*, Methicillin-susceptible *Staphylococcus aureus* and *Haemophilus influenzae* represented respectively 23%, 18% and 17% of susceptible pathogens.

In the learning cohort Methicillin resistant *Staphylococcus aureus* represented 0.7% of pathogens involved, when it was 0.8% in the validating cohort. In both cohorts, Methicillin resistant *Staphylococcus aureus* represented less than 10% of all *Staphylococcus aureus*. Repartition of pathogens found in resistant and susceptible HAP are presented in Table 3.

The mortality rate during ICU stay was 26% and in-hospital mortality rate was 29%.

In our cohort the median duration between hospitalization and pneumonia was 168 hours (7 days) [96–384], the median duration between intubation and pneumonia was 96 hours (4 days) [72–192] and the median duration between ICU admission and diagnosis of pneumonia was 96 hours (4 days) [72–216]. Figure 2 shows the different diagnosis time-periods to pneumonia.

The median length of stay in ICU was 25 days IQR[15 – 43] and 34 days IQR[21 – 60] for length of stay at hospital.

Selection of the variables of interest : Univariate analysis

Variables upheld for the construction of the scoring system were : known colonization with resistant pathogen (p=0.073), duration of antibiotic prophylaxis (p=0.146), duration of antibiotic therapy before diagnosis (p=0.033), use of carbapenem for antibiotic therapy before diagnosis (p=0.019), transfusion of red blood cells concentrate (p=0.077) and platelet concentrate (p=0.03) before diagnosis and the need for revision surgery (p=0.104). The univariate analysis in the learning cohort is shown in Table 4.

Development and validation of the scoring system : Multivariate analysis

Two factors were selected after the "backward selection method": transfusion count of platelet concentrate before diagnosis (OR 1.09, 95%CI[1.0-1.2], p=0.051), antibiotic therapy with carbapenems (OR 6.17, 95%CI[0.8-48.7], p=0.084). None of the selected variables were independently associated with the resistance to narrow-spectrum antibiotic therapy.

The multivariate analysis is shown in Table 5.

The area under the receiving operator curve for the prediction of resistance to narrow-spectrum antibiotic therapy in the validating cohort was 0.62 [0.52 – 0.75] (Figure 3).

Using a threshold of 0.64, the positive and negative predictive value were respectively 57% and 64%. Sensibility and specificity were 76% and 43% in the validating cohort. Using the predictive model, 62% of predictions were correct.

Due to a very low predictive power, we have been unable to validate the prediction model in the validating cohort.

Secondary endpoints

Compliance with common radiographical and biological criteria of hospital-acquired pneumonia are shown in Figure 4. A total of 204 (69%) of retained diagnosis by clinicians met the radiographical and biological diagnosis criteria.

Regarding the outcome of patients receiving appropriate or inappropriate empirical antibiotic therapy, no statistical difference was found between the two groups considering the development of mediastinitis ($p=0,77$), clinical of HAP recovery after ten days ($p=0.1$), length of stay in hospital ($p=0.68$) and in ICU ($p=0.42$), death rate in ICU ($p=0.54$) and in hospital ($p=0.63$). A total of 24% of patients received an inappropriate empirical antimicrobial therapy. Patients' characteristics and outcomes regarding the administration of appropriate versus inappropriate empirical antibiotic therapy are shown in Tables 6 and 7.

In our study, 69% of patients were exposed to antibiotic (therapy and prophylaxis) for at least 48 hours before pneumonia onset. A total of 37% of patients were exposed to antibiotic therapy within 90 days prior pneumonia onset (excluding perioperative antibiotic prophylaxis) and 32% for more than 48 hours. About antibiotic prophylaxis, 50% of patients have had 48 hours or more of antimicrobial prophylaxis and 50% 24 hours or less.

In the learning cohort, the most chosen empirical antibiotic therapies were Cefedipim (12%), Linezolid (11%), Meropenem (9%), Cefotaxim (9%), Amikacin (9%) and Amoxicillin-Sulbactam (9%). In the validating cohort, it was Piperacillin-Tazobactam (32%), Amikacin (18%), Vancomycin

(16%) and Amoxicillin-Sulbactam (10%). The different empirical antibiotic therapy between learning and validating cohort are shown in Table 8.

In the learning cohort, antibiotic association commonly chosen were Cefedipim only (14%), Amoxicillin-Sulbactam only (14%), Cefotaxime only (7%) Piperacillin-Tazobactam only (5%), Meropenem with Linezolid (5%). In the validating cohort it was Amoxicillin-Sulbactam only (14%), Piperacillin-Tazobactam only (12%), Piperacillin-Tazobactam with Vancomycin (11%), Cefotaxim only (10%) and Piperacillin-Tazobactam with Amikacin (10%).

<u>Discussion :</u>

In this study, we tried to develop a predictive model of bacterial resistance to empiric antibiotic therapy in HAP and VAP during post-operative period of cardiac surgery. Unfortunately, this model has a low predictive capacity, and does not perform adequately to be used in a clinical setting.

We found in our cohort a high level of bacterial resistance (68%). Our team had elaborated that a prediction score developed in brain-injured patients, who have a low level of bacteria resistance, and tested in burn victims, who have higher level of resistance, showed low predictive power in the burned population (13). The development of a predictive model for population with high levels of bacterial resistance might be more difficult.

This high level of resistance could be explained by various reasons. First, we choose to consider Enterobacteriaceae with a chromosomal inducible AmpC, the ESCPM group (*Enterobacter cloacae, Serratia marcescens, Hafnia alvei, Citrobacter Freundii, Morganella morgani, Proteus sp.*), as resistant to narrow-spectrum antibiotic therapy. An antibiotic treatment with a narrow-spectrum antibiotic therapy could led to the selection of resistant strain in this population (10). This choice may have artificially increased the number of resistant pathogens in our study while the treatment with a narrow-spectrum antibiotic therapy might have succeeded. These pathogens accounted for 27% of identified bacteria and 38% of resistant pneumonia bacteria in our cohort.

Secondary, most of pneumonia in our study were late pneumonia ($\geq$ 5 days after hospitalization). This observation matches with literature where majority of pneumonia after cardiac surgery occurred after 5 days of hospitalization. Hospital stay for 5 days or more represents an independent risk factor for developing a pneumonia (5,14). A large exposition to antibiotic therapy could have lowered the quantity of early-onset pneumonia. However, in our study,

hospital stay for 5 days or more has not been identified as a risk factor for resistant pneumonia development.

Third, in our cohort, 69% of patients were exposed to antibiotic for at least 48 hours before pneumonia onset and 50% have had an antibiotic prophylaxis of 48 hours or more. In our prior study, antibiotic therapy for 48 hours or more was an independent risk factor for developing a resistant VAP in brain injured patients (13). Literature is not clear about the right duration of antibiotic prophylaxis during cardiac surgery. Some studies and meta-analyses have shown that an antibiotic prophylaxis of 24 hours or less is inferior to longer regimens considering any type of surgical site infection (15–17). Nevertheless an antibiotic prophylaxis of more than 48 hours seems to give higher rates of antibiotic resistance in pneumonia after cardiac surgery (18).

Our study shows that inappropriate antimicrobial therapy was common in our cohort but consistent with other studies where inappropriate empirical antibiotic treatment range from 29 to 32% (19,20). Furthermore, we found no difference in clinical outcomes between patients receiving appropriate or inappropriate empirical antibiotic therapy. An inappropriate empirical antibiotic is well described as an independent risk factor for mortality and increase in ICU length of stay in severe patients. In addition, data about patients with non-severe symptoms of pneumonia in ICU (logistic organ dysfunction score ≤ 4) show difference in mortality between patients receiving inappropriate or appropriate empirical antibiotic therapy (21,22). These results could engage us to pay attention to our antibiotic usage even with non-severe patients.

In our study, we found a large amount of broad-spectrum empiric antibiotic therapy usage. There seems to be differences in habits between centres regarding the choose of antimicrobial therapy. In the learning cohort, broad-spectrum antibiotic therapy was mainly Cefedipim and Meropenem and the anti-Methicillin resistant *Staphylococcus aureus* (MRSA) was mainly Linezolid. In the validating cohort, the broad-spectrum antibiotic therapy was mainly

Piperacillin-Tazobactam and anti MRSA the vancomycin. Studies about different choice of broad-spectrum antibiotic therapy could help us to choose between those therapies.

Surprisingly, among the variables that emerged from the multivariate analysis we found the amount of transfusion with concentrate platelets before pneumonia onset. Recent studies have shown that platelets have an important role in inflammation and cellular response to infection (23). The release of antimicrobial compounds is the main mode of antibiotic action of platelets. They are also described as being able to modify the "clearance of circulating bacteria" (24). Bearing in mind that the quantity and qualitative functions of platelets are strongly altered after cardiopulmonary bypass on the one side, and the frequent need for platelet transfusion after cardiac surgery on the other, we might assume that their immunity response could be altered after cardiac surgery and especially cardiopulmonary bypass (25). There is no strong data providing a link between platelets count or ineffectiveness of platelets with development or cure of infections. Nevertheless, in specific populations like transplant patients or patients receiving anti-cancer therapy, low platelet counts are associated with a much worse prognosis and much greater likelihood of infection. Similarly, in very low birth weight premature infants with sepsis, the value and duration of thrombocytopenia and the need for platelet transfusion were associated with persistent bacteremia, multiorgan failure and death (26,27). In a large multicentre study by Brogly et *al*. (28), thrombocytopenia was an independent predictor of mortality in community acquired pneumonia in ICU. Beside these deleterious effects, some teams have shown a protective effect of platelets transfusion on post-operative infections after cardiac-surgery (29,30). This effect was particularly important when associated with a higher quantity of red blood cell transfusion. Our results are the first to establish a potential link between platelet transfusion and bacterial resistance in clinical practice. More studies are needed to evaluate this link. In the current state of knowledge, we can think that the amount of platelet transfusion may

be an unmodifiable risk factor of developing a resistant pneumonia in post-operative period of cardiac surgery.

Literature studying bacterial resistance in pneumonia after cardiac surgery is rare. There is evidence that antibiotic therapy before pneumonia onset is the most important factor associated with isolation of resistant microorganism in post-operative pneumonia (31). The development of pneumonia after major heart surgery has a significant impact on patient's outcomes. Mortality rates in patients developing pneumonia after cardiac surgery range from 14 to 33% (3). The mortality rate and hospital or ICU length of stay in our study are in line with other studies that have shown comparable data on patients developing HAP or VAP (32–34). It is not clear whether or not the antimicrobial resistance has an impact on outcomes of patients undergoing cardiac surgery. One study by Allou N et. *al* (31) showed increased mortality in patient receiving an inappropriate antimicrobial therapy in this context.

Our study is the first which analysed the resistance to antibiotic therapy in pneumonia after cardiac surgery. However, it has several limitations. The retrospective design may have included some selection bias. Our analysis of compliance to radiographical and biological criteria of pneumonia diagnosis showed that a significant amount of pneumonia didn't match those criteria. This may have led to the treatment and analysis of tracheobronchitis which does not follow the same guidelines (35). A limited number of patients and a large amount of bacterial resistance may have decreased the power of the predictive model.

Conclusion :

Diagnosis and empirical treatment of pneumonia during post-operative period of cardiac surgery remain an important issue within a global context of increasing bacterial resistance.

In order to improve our capacity to limit our use of broad-spectrum antibiotics, more cohorts are required to propose an adequate predictive score to use narrow-spectrum antibiotics. Furthermore, we have to challenge our practices regarding antibiotic therapy and prophylaxis in the perioperative period of cardiac surgery. Our study showed a significant use of antibiotic agent against methicillin resistant *Staphylococcus aureus* (Linezolid and Vancomycin), even though in both cohorts the incidence of this pathogen was less than 1% and less than 10% of all *Staphylococcus aureus*. A first step could be to reduce our utilization of these antibiotic therapies.

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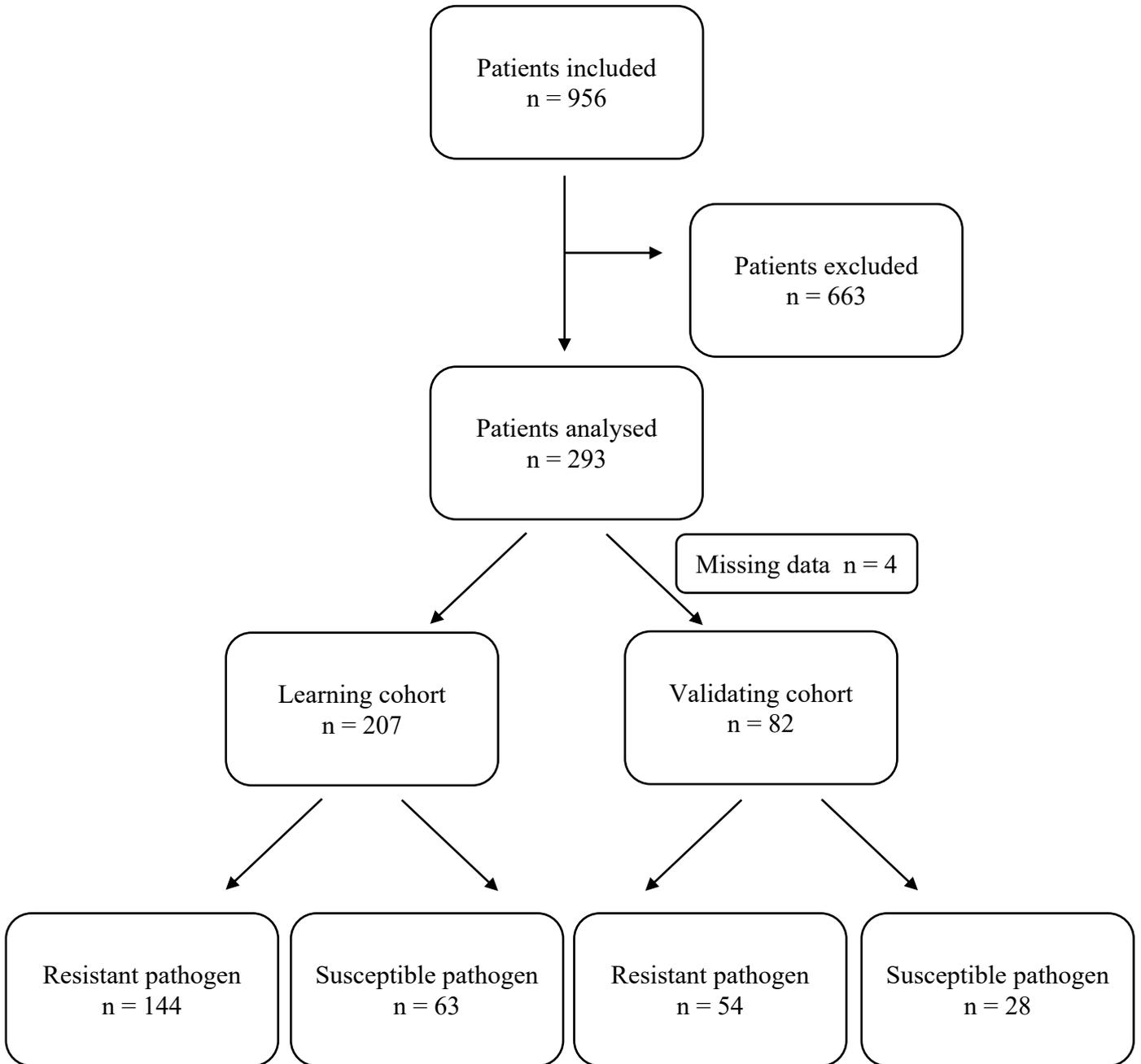
Figure 1 : Flowchart

Table 1 : Baseline characteristics

	Learning Cohort n = 207	Validating Cohort n = 82	p value
Age (years)	65 [56 – 72]	64 [57 – 70.5]	0.79
Euroscore II (%)	5.87 [2.80 – 13.62]	9.76 [2.67 – 26.46]	0.026
SAPS II	46.2 (12.3)	46.2 (14.1)	0.99
Sex (male)	163 (78)	66 (79)	0,84
BMI (kg/m^2)	26.6 (4.9)	26 (4.4)	0.27
Pre-operative Haemoglobin (g/dL)	13.2 (2.2)	13.1 (2.2)	0.8
Pre-operative LVEF [a]			0.01
< 20%	12 (6)	13 (16)	
20-30%	28 (14)	4 (5)	
30-49%	32 (16)	12 (14)	
≥ 50%	126 (63)	54 (65)	
Beta-blocker treatment	82 (39)	38 (46)	0.36
COPD	28 (13)	12 (14)	0.95
Steroid treatment	14 (7)	3 (4)	0.41
Immune deficiency	47 (22)	13 (16)	0.26
Myocardial infarction	22 (10)	25 (30)	<0.01
Tobacco	27 (13)	22 (27)	<0.01
Diabetes	39 (19)	14 (17)	0.86
High blood pressure	97 (46)	54 (65)	<0.01
Dialysed chronic renal failure	1 (0.4)	0	1
Known resistant bacterial colonization	10 (5)	5 (6)	0.6

Data are presented as n, n (%), median [Interquartile Range], Mean (SD). [a]: According to the Euroscore II classification (12). Percentages may not add up to 100 due to rounding. COPD*: Chronic Obstructive Pulmonary Disease.* LVEF*: Left Ventricular Ejection Fraction. Immune deficiency : hemopathy, AIDS, cancer, diabetes, graft. Known resistant bacterial colonization : cutaneous sample or history of infection.*

Table 2 : Surgery types in learning and validating cohort

	Learning Cohort n = 352	Validating Cohort n = 109
Aortic valve replacement - biological	11% (39)	14% (15)
Mitral valve replacement - biological	11% (37)	4% (4)
Heart transplant	9% (30)	7% (8)
Tricuspid valve repair	8% (28)	2% (2)
Maze procedure	5% (17)	1% (1)
Mitral valve repair	5% (17)	3% (3)
Bentall procedure - biological	5% (16)	4% (4)
CABG : Two	5% (16)	7% (8)
Bi-pulmonary transplant	4% (15)	-
CABG : One	4% (15)	7% (8)
CABG : Four	4% (15)	2% (2)
Total aortic arch replacement	4% (13)	1% (1)
Supra coronary tube replacement	4% (13)	6% (7)
Left ventricular assistive device	3% (10)	4% (4)
Mitral valve replacement – mechanical	8% (2)	0% (0)
Central ECLS	2% (6)	-
CABG : Three	2% (6)	9% (10)
Bentall procedure - mechanical	1% (5)	3% (3)
Aortic valve replacement - mechanical	1% (4)	3% (3)
Atrial septal defect	1% (3)	-
Bi-ventricular replacement device	1% (3)	-
Peripheral ECLS	1% (3)	7% (8)
Hemi aortic arch replacement	1% (3)	7% (8)
Pulmonary valve replacement – all types	1% (3)	-
Tricuspid valve replacement – all types	1% (3)	1% (1)
Tirone-Davie procedure	1% (3)	-
Intracardiac tumour	1% (3)	-
Aortic valve repair	1% (2)	-
CABG : Five	<1% (1)	-
Pericardiectomy	<1% (1)	-
Ventricular septal defect	-	1% (1)
Elephant trunk procedure	-	2% (2)
Pneumonectomy	-	2% (2)
Others	4% (14)	4% (4)
Surgery category		
Isolated CABG	9%	20%
One procedure other than CABG	11%	28%
Two procedures	20%	8%
Three procedures or more	13%	4%
Thoracic aorta Surgery	20%	25%
Cardiac Assist	6%	5%
Graft	21%	10%

Data are presented as % (n) or %. Total may not add up to 100% because of rounding. CABG : Coronary Arterial Bypass Grafting. ECLS : Extra Corporeal Life Support.

Table 3 : Microorganism susceptibility or resistance to narrow-spectrum antibiotic therapy

	Learning Cohort	Validating Cohort
Susceptible to Narrow-spectrum antibiotic therapy	100% (74)	100 % (39)
Escherichia coli	27% (20)	15% (6)
Methicillin-susceptible *Staphylococcus aureus*	20% (15)	15% (6)
Haemophilus influenzae	19% (14)	15% (6)
Klebsiella oxytoca	9% (7)	13% (5)
Citrobacter koseri	5% (4)	5% (2)
Proteus Mirabilis	5% (4)	0
Streptococcus pneumoniae	4% (3)	10% (4)
Klebsiella pneumoniae	1% (1)	10% (4)
Others	7% (6)	15% (6)
Resistant to narrow-spectrum antibiotic therapy	100% (187)	100% (82)
Pseudomonas aeruginosa	17% (31)	30% (25)
Enterobacter cloacae	14% (26)	12% (10)
Hafnia alveii	11% (21)	6% (5)
Serratia marcescens	11% (20)	9% (7)
Escherichia coli	7% (14)	6% (5)
Haemophilus Influenzae	5% (9)	6% (5)
Klebsiella pneumoniae	5% (9)	2% (2)
Morganella morganii	4% (7)	2% (2)
Enterococcus faecalis	4% (7)	0
Enterobacter aerogenes	4% (7)	2% (2)
Proteus mirabilis	3% (5)	4% (3)
Citrobacter freundii	1% (2)	4% (3)
Others	16% (30)	16% (13)

Data are presented as % (n)
Pathogens shown in this table may not be directly resistant to narrow spectrum antibiotic therapy but considered as resistant due to multiple pathogen pneumonia.
Percentage may not add up to 100 because of rounding.

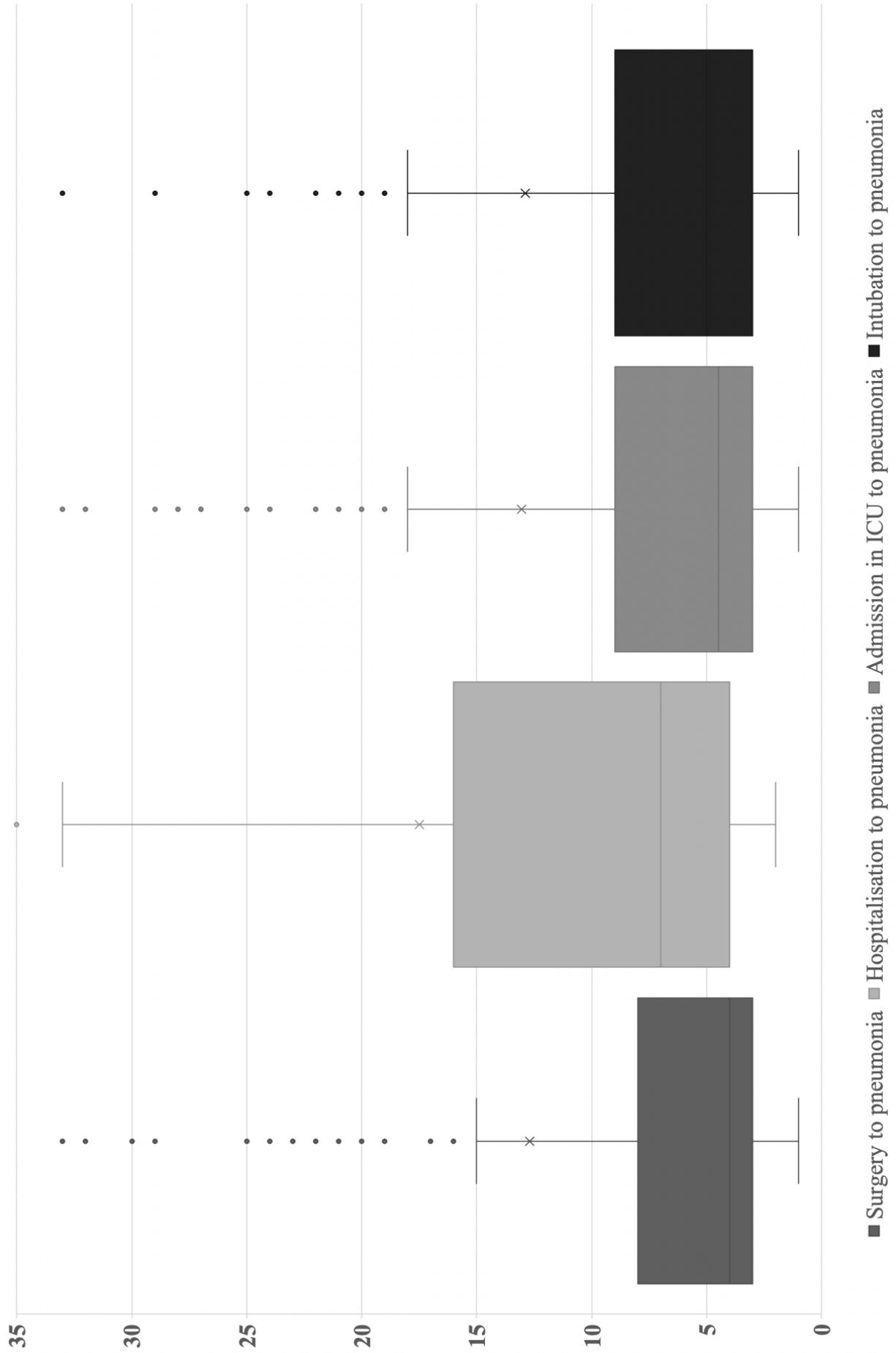**Figure 2 : Time-periods for pneumonia onset (days)**

Table 4 : Univariate analysis in the learning cohort

	Narrow-spectrum sensibility n = 63	Narrow-spectrum resistance n = 144	P value
Age (Years)	63 (13)	63 (1)	0.88
Euroscore II (%)	5.5 [3 - 14]	6.2 [3 - 12]	0.65
SAPSII	47.7 (13)	45.56 (15)	0.33
Sex (Male)	45 (71)	115 (80)	0.25
BMI (kg/m^2)	26.76 (5)	26.58 (5)	0.81
Pre-operative Hemoglobin (g/dL)	13.45 (2)	13.05 (2)	0.24
Pre-operative LVEF (%)	60 [28 - 65]	53 [35 - 60]	*0.18
Beta-blocker treatment	24 (38)	58 (40)	0.89
Hospitalization in past 3 months	38 (60)	73 (51)	0.26
Transfer from another hospital	16 (25)	34 (24)	0.92
COPD	7 (11)	21 (15)	0.65
Steroid treatment	2 (3)	11 (8)	0.36
Immune deficiency [c]	12 (19)	34 (24)	0.59
Myocardial infarction	7 (11)	15 (10)	1
Tobacco	9 (14)	18 (13)	0.9
Diabetes	10 (16)	28 (19)	0.68
High Blood Pressure	27 (43)	69 (48)	0.6
Dialysed chronic renal failure	0 (0.0)	1 (0.7)	1
Known colonisation with resistant pathogen	0 (0.0)	10 (7)	*0.07
Surgery delay			0.65
Elective	29 (46)	66 (46)	
Urgent (< 7 days)	6 (10)	20 (14)	
Emergency (< 24 hours)	28 (44)	58 (40)	
Surgery classification			0.25
Isolated CABG	5 (8)	13 (9)	
One procedure other than CABG	12 (19)	11 (8)	
Two procedures	12 (19)	28 (19)	
Three procedures or more	10 (16)	18 (13)	
Thoracic aorta Surgery	11 (18)	30 (21)	
Cardiac Assist	2 (3)	11 (8)	
Graft	11 (18)	33 (23)	
Redo surgery	11 (18)	29 (20)	0.8
Hypothermia during CPB ≤ 34°C	7 (11)	17 (12)	1
CPB duration (min)	164 (77)	178.47 (83)	0.27
Clamping duration (min)	101 [65 - 139]	101[79 - 140]	0.72
Circulatory arrest (min)	0 [0 - 0]	0 [0 - 0]	0.62
Intra operative transfusion			
Globular concentrate	2 [0 - 4]	2 [0 - 5]	0.24
Frozen plasma	3 [0 - 6]	3 [0 - 8]	0.38
Patelet concentrate	1 [0 - 1]	1 [0 - 2]	*0.18
Before pneumonia transfusion			
Globular concentrate	6 [2 - 12]	8 [3 - 17]	*0.08
Frozen plasma	7 [3 - 12]	8 [3 - 15]	0.24

Patelet concentrate	1 [0 - 3]	2 [0.8 - 5]	*0.03
Revision surgery	27 (43)	81 (56)	*0.1
SOFA score at admission in ICU	8 [6 - 10]	8 [6 - 9]	0.98
Antibiotic therapy [a]			
Duration (Days)	0 [0 - 6]	0 [0 - 8]	*0.03
Penicillin, 1st/2nd generation cephalosporin	15 (24)	60 (42)	*0.02
Quinolone	1 (2)	5 (4)	0.77
3rd or 4th generation cephalosporin	6 (10)	24 (17)	0.26
Carbapenem	1 (2)	19 (13)	*0.019
Antibiotic prophylaxis [a]			
Antibiotic prophylaxis duration (days)	2 [1 - 2]	2 [1 - 2]	*0.15
Nasal decontamination	0 [0 - 0]	0 [0 - 0]	-
Penicillin, 1st/2nd generation cephalosporin	58 (94)	118 (85)	*0.14
3rd generation cephalosporin	1 (2)	0 (0)	0.68
Carbapenem	1 (2)	1 (0.7)	1
Maximal temperature [b] (°C)	37.9 [37.5 - 38.6]	37.8 [37.2 - 38.4]	0.23
Leucocytes numeration [b] (G/L)	13 [9.5 - 18]	14 [10 - 19]	0.45
PaO2 / FiO2 [b]	197 [153 - 258]	207 [154 - 289]	0.55
Number of lung lobe affected on X-ray [b]			0.5
0	2 (3)	2 (1)	
1	35 (57)	79 (56)	
2	23 (37)	45 (32)	
3	2 (3)	10 (7)	
4	0 (0)	2 (1)	
5	0 (0)	3 (2)	
Mechanical ventilation [a] (days)	5 [4 – 8]	5 [4 - 10]	0.54
Dialysis [a] (days)	3 [0 - 5]	3 [0 - 5]	0.66
Catecholamines [a] (days)	5 [4 - 7]	5 [3 - 8]	0.83
Cardiac Assist [a] (days)	0 [0 - 4]	0 [0 - 4]	0.37
Peripheral ECLS[d]	10 (63)	25 (49)	0.51
Surgery to pneumonia period (hours)	120 [84 - 192]	120 [72 - 216]	0.54
Hospitalization – pneumonia period (hours)	192 [120 - 324]	180 [96 - 438]	0.91
ICU admission to pneumonia period (hours)	120 [96 - 19]	120[72 - 264]	0.83
Intubation to pneumonia period (hours)	120 [78 - 192]	120 [72 - 240]	0.71

Data are presented as n, median [interquartile range], n (%) or mean (SD), unless otherwise stated.

* : p<0.2

[a] : Before pneumonia diagnosis

[b] : On the day of pneumonia diagnosis

[c] : Hemopathy, graft, AIDS, diabetes, cancer

[d] : Peripheral Vs Central Extracorporeal Life Support

COPD : Chronic Obstructive Pulmonary Disease. CPB : CardioPulmonary Bypass. LVEF : Left Ventricular Ejection Fraction. ICU : Intensive Care Unit. ECLS : ExtraCorporeal Life Support

Table 5 : Multivariate analysis, Initial and final model

	Crude OR	Adjusted OR	p value
<u>Initial model</u>			
Know colonization	-	-	-
Antibiotic therapy [a]	1.02 [0.99 – 1.05]	0.98 [0.94 – 1.02]	0.25
Blood transfusion [a]	1.05 [1.01 – 1.08]	0.99 [0.93 - 1,05]	0.77
Platelets transfusion [a]	1.12 [1.02 – 1.23]	1.12 [0.96 – 0.3]	0.15
Revision surgery	1.71 [0.94 – 3.12]	1.40 [0.71 – 2.78]	0.33
Antibiotic therapy : carbapenems	9.42 [1.23 – 72.02]	9.12 [0.87 – 95.42]	0.07
Antibiotic prophylaxis time-period	0.72 [0.50 – 1.04]	0.71 [0.46 – 1.08]	0.11
<u>Final model</u>			
Know colonization	-	-	-
Platelets transfusion [a]	1.12 [1.02 – 1.23]	1.09 [1 – 1.20]	0.05
Antibiotic therapy : carbapenems	9.42 [1.23 – 72.02]	6.17 [0.78 – 48.71]	0.08

Data are presented as OR [95% CI]
[a] : Before pneumonia onset

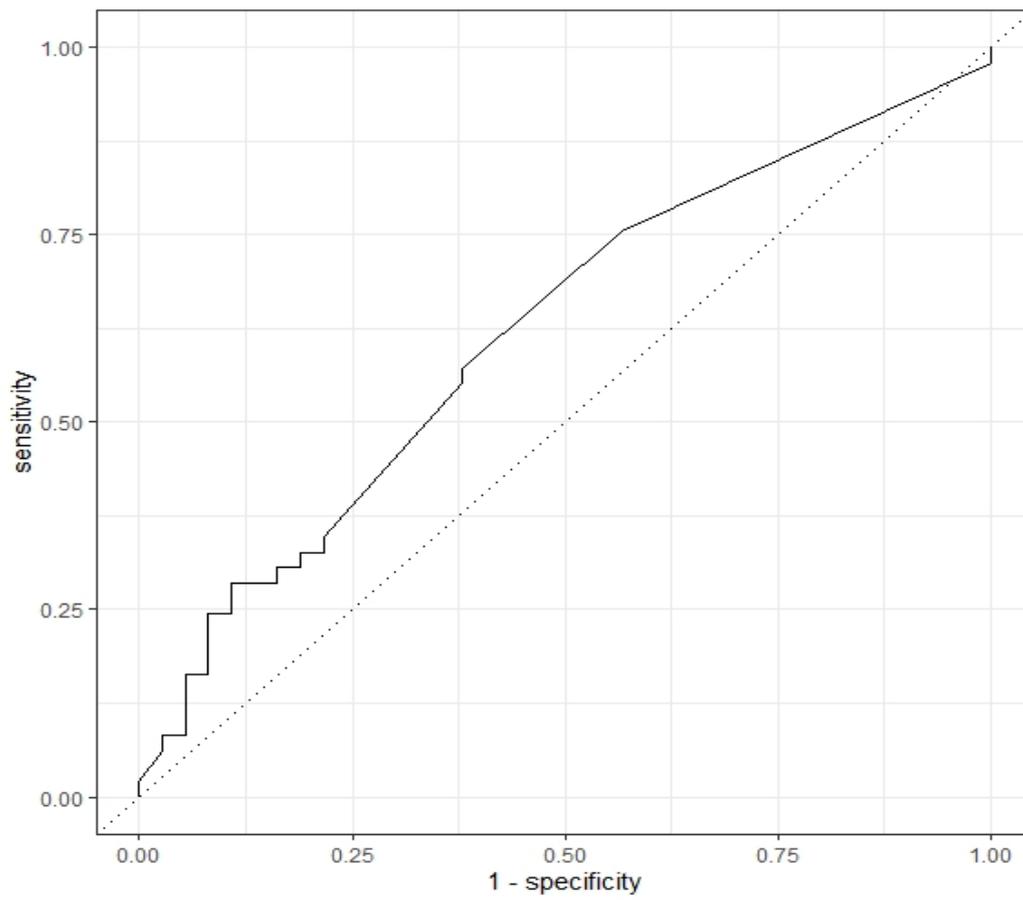**Figure 3 : ROC Curve associated with prediction model**

Figure 4 : Compliance with diagnosis criteria of hospital-acquired pneumonia
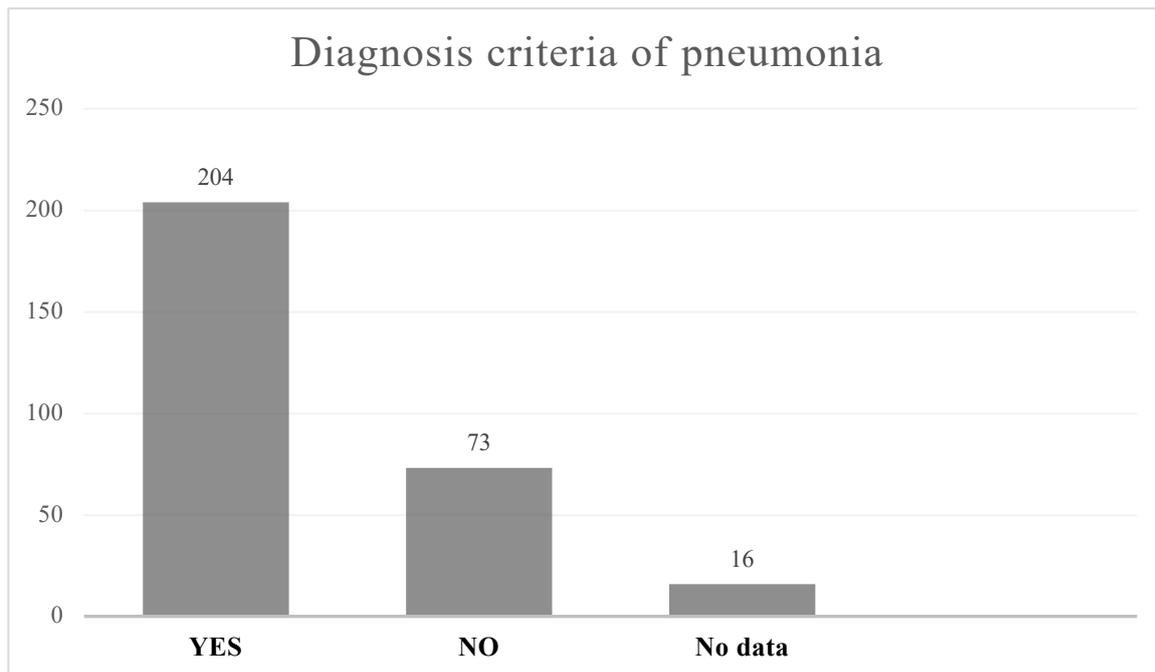
Radiological and biological criteria for diagnosis of hospital-acquired pneumonia according to Leone M et al. (36) (Two successive chest radiographs showing new or progressive lung infiltrates In the absence of medical history of underlying heart or lung disease, a single chest radiograph is enough, and at least one of the following signs : Body temperature > 38,3 °C without any other cause, Leucocytes < 4000/mm³ or ≥ 12,000/mm.)

Table 6 : Characteristics of patients receiving appropriate or inappropriate empirical antimicrobial therapy

	Appropriate n = 222	Inappropriate n = 69	p value
Age (Years)	63 ± 13	62 ± 12	0.82
Euroscore II (%)	7 [3 – 17]	7 [3 – 15]	0.54
IGSII	45 [36 – 54]	46 [38 – 57]	0.37
Sex (Male)	167 (75)	60 (87)	0.06
BMI (kg/m^2)	26 [23 – 29]	26 [23 – 31]	0.36
Pre-operative Haemoglobin (g/dL)	13.4 [12 – 15]	13.3 [12 – 15]	0.49
Pre-operative LVEF [a]			0.1
< 20 %	19 (9)	6 (9)	
20 – 29 %	26 (12)	5 (8)	
30-49 %	39 (18)	5 (8)	
≥ 50 %	130 (61)	49 (75)	
Beta-blocker treatment	84 (38)	35 (51)	0.08
COPD	30 (14)	9 (13)	1
Steroid treatment	14 (6)	3 (4)	0.77
Immune deficiency	47 (21)	13 (19)	0.8
Myocardial infarction	37 (17)	9 (13)	0.59
Tobacco	40 (18)	9 (13)	0.44
Diabetes	39 (18)	14 (20)	0.74
High Blood Pressure	111 (50)	39 (57)	0.42
Dialysed chronic renal failure	1 (<1)	-	-
Known resistant bacterial colonization	13 (6)	1 (1)	0.2
Hospitalization in previous 3 months	130 (59)	33 (48)	0.15
Transfer from another hospital	64 (29)	17 (25)	0.6
Redo surgery	40 (18)	9 (13)	0.44
Hypothermia during CPB	29 (13)	13 (19)	0.34
Revision surgery	103 (46)	43 (62)	*0.03
ECLS type			0.25
Peripheral ECLS	49 (22)	10 (15)	
Central ECLS	33 (15)	10 (15)	
Nasal Decontamination	16 (7)	3 (4)	0.58
Surgery Programming			0.63
Elective	102 (46)	32 (46)	
Urgent (< 7 days)	32 (14)	7 (10)	
Emergency (< 24 hours)	88 (40)	30 (43)	
Surgery category			0.11
Isolated CABG	29 (13)	6 (9)	
One procedure other than CABG	40 (18)	5 (7)	
Two procedures	35 (16)	13 (19)	
Three procedures or more	20 (9)	11 (16)	
Thoracic aorta Surgery	43 (19)	20 (29)	
Cardiac Assist	13 (6)	3 (4)	
Graft	42 (19)	11 (16)	
CPB duration (min)	151 [95 – 195]	163 [124 – 215]	*0.03
Clamping duration (min)	84 [49 – 116]	115 [85 – 146]	*<0.001
Circulatory arrest (min)	0 [0 – 0]	0 [0 – 0]	0.35
Surgery Duration (min)	297 [231 – 412]	330 [254 – 409]	0.83

<u>Intra operative transfusion</u>			
Globular concentrate	2 [0 – 4]	2 [0 – 4]	0.6
Frozen plasma	3 [0 – 6]	3 [0 – 7]	0.51
Patelet concentrate	1 [0 – 1]	0 [0 – 2]	0.42
<u>Before pneumonia transfusion</u>			
Globular concentrate	6 [2 – 11]	6 [2 – 11]	0.54
Frozen plasma	5 [1 – 10]	7 [4 – 12]	0.52
Patelet concentrate	1 [0 – 3]	2 [0 – 3]	0.7
SOFA at ICU admission	8 [6 – 9]	8 [6 – 9]	0.88
Hospitalization to pneumonia delay (hours)	168 [120 – 402]	168 [96 – 336]	0.27
Intubation to pneumonia delay (hours)	120 [72 – 216]	84 [66 – 168]	0.38
Surgery to pneumonia delay (hours)	120 [72 - 210]	96 [72 – 210]	0.08
ICU admission to pneumonia delay (hours)	120 [72 – 216]	72 [48 – 168]	0.09
<u>Antibiotic therapy</u> [c]			
Duration (Days)	0 [0 – 6]	0 [0 – 4]	0.25
Penicillin, 1st/2nd generation cephalosporin	67 (30)	22 (32)	0.90
Quinolone	4 (2)	2 (3)	0.63
3rd or 4th generation cephalosporin	32 (14)	3 (4)	0.04
Carbapenem	15 (7)	4 (6)	1
<u>Antibiotic prophylaxis</u> [c]			
Antibiotic prophylaxis duration (days)	1 [1 – 2]	2 [1 -2]	0.78
Nasal decontamination	16 (7)	3 (4)	0.58
Penicillin, 1st/2nd generation cephalosporin	190 (88)	61 (90)	0.79
3rd generation cephalosporin	1 (<1)	2 (3)	0.14
Carbapenem	2 (1)	2 (3)	0.24
Maximal temperature [b] (°C)	38.1 [37.4 – 38.6]	37.9 [37.2 – 38.5]	0.2
Leucocytes numeration [b] (G/L)	13.5 [10 – 19]	13.1 [10 -18]	0.51
PaO2 / FiO2 [b]	186 [130 – 257]	184 [153 – 255]	0.62
<u>Number of lung lobe affected on X-ray</u> [b]			0.71
0	3 (1)	2 (3)	
1	134 (61)	37 (54)	
2	62 (28)	24 (35)	
3	14 (6)	5 (7)	
4	2 (<1)	-	
5	3 (1)	1 (<1)	
Dialysis [c] (days)	0 [0 – 5]	1 [0 – 3]	0.06
Catecholamines [c] (days)	5 [3 – 8]	4 [3 – 6]	0.20
Cardiac Assist [c] (days)	0 [0 – 3]	0 [0 – 2]	0.07

Data are presented as n, median [interquartile range], n (%) or mean ± SD.
* : p<0.05
[a] : According to Euroscore II (12)
[b] : At pneumonia onset
[c] : Before pneumonia onset
COPD : Chronic Obstructive Pulmonary Disease. CPB : CardioPulmonary Bypass. LVEF : Left Ventricular Ejection Fraction. ICU : Intensive Care Unit. ECLS : ExtraCorporeal Life Support

Table 7 : Outcomes of patients receiving appropriate or inappropriate empirical antimicrobial therapy

	Appropriate n = 222	Inappropriate n = 69	p value
Mediastinitis	24 (11)	6 (9)	0.77
Healed at 10 days of pneumonia onset	136 (61)	34 (49)	0.1
ICU stay (days)	25 [15 – 42]	26 [17– 49]	0.42
Mechanical ventilation (days)	15 [7 – 27]	20 [12 – 40]	0.57
Duration of hospitalization (hours)	816 [504 – 1392]	936 [576 – 1800]	0.83
Surgery to hospital exit	720 [432 – 1200]	792 [432 – 1656]	0.64
Intubation to hospital exit (hours)	708 [408 – 1182]	792 [426 – 1530]	0.77
ICU admission to hospital exit (hours)	708 [432 – 1272]	816 [480 – 1656]	0.68
Pneumonia onset to hospital exit (hours)	576 [288 – 1008]	658 [240 – 1272]	0.78
In-ICU mortality	54 (24)	20 (29)	0.54
In-hospital mortality	62 (28)	22 (32)	0.63

Data are presented as n, median [interquartile range], n (%) or mean ± SD. ICU : Intensive Care Unit

Table 8 : Empirical antibiotic therapy in the learning and validating cohort

	Learning n=346	Validating n=148	Total n=494
Penicillins			
A / M	36 (10%)	17 (11%)	53 (11%)
Amoxicillin	5 (1%)	1 (<1%)	6 (1%)
Amoxicillin + Sulbactam	30 (9%)	15 (10%)	45 (9%)
Cloxacillin	1 (<1%)	1 (<1%)	2 (<1%)
Carboxy / ureido penicillins	38 (11%)	48 (32%)	86 (17%)
Ticarcillin	1 (<1%)	0	1 (<1%)
Piperacillin + Tazobactam	36 (10%)	48 (32%)	84 (17%)
Ticarcillin + sulbactam	1 (<1%)	0	1 (<1%)
Others			
Temocillin	1 (<1%)	0	1 (<1%)
Cephalosporins			
3rd generation	55 (16%)	14 (9%)	69 (14%)
Ceftazidim	9 (3%)	4 (3%)	13 (3%)
Cefotaxim	31 (9%)	9 (6%)	40 (8%)
Ceftriaxone	14 (4%)	1 (<1%)	15 (3%)
Ceftolozane + Tazobactam	1 (<1%)	0	1 (<1%)
4th generation			
Cefepidim	42 (12%)	1 (<1%)	43 (9%)
Carbapenems	37 (11%)	3 (2%)	40 (8%)
Imipenem	7 (2%)	3 (2%)	10 (2%)
Meropenem	30 (9%)	0	30 (6%)
Aminoglycosides	52 (15%)	37 (25%)	89 (18%)
Amikacin	30 (9%)	27 (18%)	57 (12%)
Gentamycin	17 (5%)	10 (7%)	27 (5%)
Tobramycin	5 (1%)	0	5 (1%)
Fluoroquinolones	12 (3%)	1 (<1%)	13 (3%)
Ciprofloxacin	9 (3%)	0	9 (2%)
Levofloxacin	3 (1%)	1 (<1%)	4 (<1%)
Glycopeptides			
Vancomycin	4 (1%)	23 (16%)	27 (5%)
Macrolides			
Rovamycin	1 (<1%)	0	1 (<1%)
Clindamycin	0	1 (<1%)	1 (<1%)
Nitroimidazoles			
Metronidazole	17 (5%)	0	17 (3%)
Monobactam			
Aztreonam	1 (<1%)	0	1 (<1%)
Others			
Linezolid	39 (11%)	4 (3%)	43 (9%)
Sulfamethoxazole – trimethoprim	1 (<1%)	0	1 (<1%)
Colimicine	6 (2%)	0	6 (1%)
Daptomycin	4 (1%)	0	4 (<1%)

Data are presented as n, n (%). Percentage may not add up to 100% because of rounding

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NOM : LECOMTE   PRENOM : Jules

Titre de Thèse :

Facteurs de risque de résistance bactérienne des pneumonies liées aux soins en post-opératoire de chirurgie cardiaque
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Risk factors for bacterial resistance in hospital-acquired pneumonia after major heart surgery

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RÉSUMÉ

Introduction : La pneumonie en post-opératoire de chirurgie cardiaque reste à ce jour l'infection liée au soin la plus fréquente dans ce contexte. Les cliniciens sont confrontés quotidiennement au choix d'une antibiothérapie probabiliste à large spectre ou à spectre étroit. Notre objectif principal était de développer un score clinique utilisable au lit du patient permettant de prédire la résistance bactérienne des pneumonies nosocomiales en post-opératoire de chirurgie cardiaque. Nos objectifs secondaires étaient de décrire l'épidémiologie des pneumonies et analyser les pratiques et le devenir des patients.
Méthode : Nous avons conduit une étude rétrospective multicentrique dans trois centres universitaires en France. Les patients inclus devaient subir une chirurgie cardiaque avec circulation extracorporelle. Le diagnostic de pneumonie était réalisé par les cliniciens et une analyse quantitative de prélèvements du tractus ventilatoire avec antibiogramme était réalisée. Deux cohortes ont été construites : une « cohorte d'apprentissage », pour développer le score et une « cohorte de validation », pour confirmer sa performance. Les variables d'intérêt ont été sélectionnées via une analyse univariée. Nous avons ensuite construit le modèle prédictif à partir de ces variables grâce à une régression logistique.
Résultats : 293 patients ont été inclus, 207 dans la cohorte d'apprentissage et 82 dans la cohorte de validation. L'air sous la courbe produite par le modèle prédictif était de 0,62. Il n'a pas été possible de créer un modèle prédictif solide. Nous n'avons pas mis en évidence de différence dans le devenir des patients selon qu'ils recevaient une antibiothérapie empirique adaptée ou non.

ABSTRACT

Background : Pneumonia remains the most frequent infection in the peri-operative period of cardiac surgery and has an important negative impact on outcomes of patients. Clinicians are challenged in their choice between narrow and broad-spectrum empirical antibiotic therapy. Our primary objective was to develop and validate a clinical, bed-side compatible, predictive score of bacterial resistance in this context. Our secondary objectives were to describe the epidemiology of pneumonia after cardiac surgery and analyse clinical practices and patient's outcomes.
Method : We performed a multicentre retrospective study in three university centres in France. Patients undergoing cardiac surgery with cardiopulmonary bypass were eligible. The diagnosis of pneumonia was performed by the clinician and a quantitative respiratory tract sample was necessary. Two cohorts were created: the "learning cohort" to develop the score and the "validating cohort" to validate its capacities. Univariate analysis was performed to select variables of interest. We then built the predictive model from these variables with a logistic regression method.
Results : 293 patients were included, 207 in the learning cohort and 82 in the validating cohort. The area under the curve of the predictive model was 0.62. It has not been possible to create a solid predictive model. No difference in outcomes was found between appropriate and inappropriate empiric antimicrobial therapy.

MOTS-CLES
- VAP, HAP, pneumonia, major heart surgery, antimicrobial resistance
- PAVM, pneumonie, Chirurgie cardiaque, Résistance bactérienne