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**Mortality attributable to hospital-acquired infection after cardiac surgery.**

Nicolas MASSART, MD<sup>1,2,3</sup>, Alexandre MANSOUR, MD<sup>1,2</sup>, James T. ROSS, MD<sup>4</sup>, Caroline PIAU, MD<sup>5</sup>, Jean-Philippe VERHOYE, MD, PhD<sup>6</sup>, Pierre TATTEVIN MD, PhD<sup>7</sup>, Nicolas NESSELER, MD, PhD<sup>1,8,9</sup>

<sup>1</sup>Department of Anesthesia and Critical Care, Pontchaillou, University Hospital of Rennes, 2, rue Henri le Guilloux 35000 rennes, France

<sup>2</sup>Univ Rennes, CHU de Rennes, F-35000 Rennes, France

<sup>3</sup>Intensive Care-Unit, Hospital of St Briec, 10 rue Marcel Proust 22000 Saint-Briec, France

<sup>4</sup>Department of Surgery, University of California, San Francisco, USA

<sup>5</sup> Department of Clinical Microbiology, Rennes University Hospital, 2, rue Henri le Guilloux 35000 rennes, France.

<sup>6</sup>Thoracic and Cardiovascular Surgery Service, Pontchaillou University Hospital Center, University of Rennes 1, Signal and Image Treatment Laboratory (LTSI), National Institute of Health and Medical Research U1099, Rennes, France.

<sup>7</sup>Infectious Diseases and Intensive Care Unit, Pontchaillou University Hospital, Rennes, France.

<sup>8</sup>Univ Rennes, CHU de Rennes, Inra, Inserm, Institut NUMECAN – UMR\_A 1341, UMR\_S 1241, F-35000 Rennes, France

<sup>9</sup>Univ Rennes, CHU Rennes, Inserm, CIC 1414 (Centre d'Investigation Clinique de Rennes), F35000 Rennes, France

**Corresponding author :**

Dr. Nicolas Nessler, Hôpital Pontchaillou, Pôle Anesthésie, SAMU, Urgences,  
Réanimations, Médecine Interne et Gériatrie (ASUR-MIG), rue Henri Le Guilloux, 35033  
Rennes Cedex 9, France.  
Tel.: 33.2.99.28.42.46; Fax: 33.2.99.28.24.21; E-mail: [nicolas.nesseler@chu-rennes.fr](mailto:nicolas.nesseler@chu-rennes.fr)

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**Access to data**

Data are available from corresponding authors on reasonable demand.

**Contribution**

CPC, JPV, NN and NM contributed to the acquisition of data. NN, and NM conducted the statistical analysis, contributed to the study conception and design as well as the analysis and interpretation of the data. NN, AM, JTR and NM drafted the manuscript, and all authors critically revised the manuscript and approved the final version.

**IRB number and date of approval**

The local IRB (« comité d'éthique du CHU de Rennes ») approved the study (N°19.53) the 12 of may 2019.

## Mortality attributable to hospital-acquired infections after cardiac surgery



8,853 patients



Cardiac surgery



2012-2019

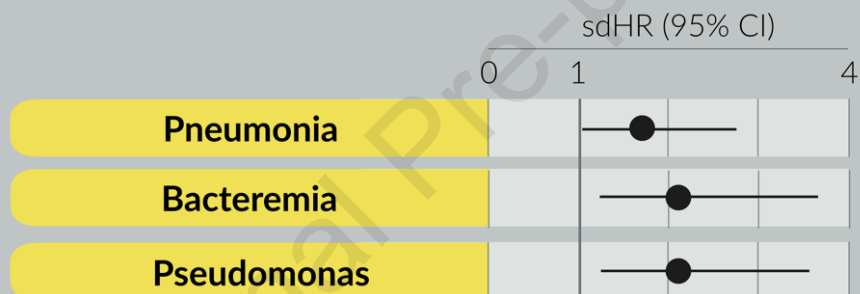
**Postoperative infections**

4 %

**Attributable mortality**

17 %

### In hospital mortality in patients with hospital-acquired

**Low incidence but major impact on postoperative mortality**

1 **Central message :**

2 Patients with HAI after cardiac surgery have a higher risk for death, especially in patients  
3 with *Pseudomonas aeruginosa* infection, acquired bloodstream infection or acquired  
4 pneumonia.

5 **Perspective Statement :**

6 Few is known about HAI attributable mortality after cardiac surgery. We conducted a  
7 Propensity-score matched analysis that allowed the estimation of HAI attributable mortality  
8 fraction. Although few patients developed HAI (4.2%), attributable mortality fraction is high  
9 (17.1%).

10 **Abbreviated legend for Central Picture**

11 Mortality attributable to hospital-acquired infections (HAI) after cardiac surgery

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19 **ABSTRACT**20 **Purpose:**

21 Hospital acquired infections (HAI) have been associated with significant morbidity and  
22 mortality in critically ill surgical patients. However, little is known about HAI-attributable  
23 mortality in cardiac surgery.

24 **Material and Methods:**

25 We conducted a retrospective analysis of prospectively collected data from the cardiac  
26 surgery unit of a university hospital. All patients who underwent cardiac surgery over a seven-  
27 year period were included. Patients with HAI were matched 1:1 with non-HAI patients based  
28 on risk factors for HAI and death after cardiac surgery, using propensity-score matching. We  
29 performed a competitive risk analysis to study the HAI-attributable mortality fraction.

30 **Results:**

31 Of 8,853 patients who underwent cardiac surgery, 370 (4.2%) developed 500 post-operative  
32 infections (incidence density rate 4.2 HAI per 1,000 patient-days). Crude hospital mortality  
33 was significantly higher in HAI patients than in matched patients who did not develop HAI,  
34 15.4% and 5.7% respectively ( $p < 0.001$ ). The in-hospital mortality fraction attributable to  
35 HAI in our cohort was 17.1 % [12.3% – 22.8%]. *Pseudomonas aeruginosa* infection (HR =  
36 2.09; 95% CI [1.23-3.49];  $p = 0.005$ ), bloodstream infection (HR = 2.08; 95% CI [1.19–3.63]  
37  $p = 0.010$ ) and pneumonia (HR = 1.68; 95% CI [1.02–2.77];  $p = 0.04$ ) were each  
38 independently associated with increased hospital mortality.

39 **Conclusion:**

40 While HAIs are relatively uncommon after cardiac surgery (4.2%), these infections have a  
41 major impact on post-operative mortality (attributable mortality fraction 17.1%).

42

43 **Keywords:** Hospital-acquired pneumonia; Bacteremia; Surgical site infection; Mortality;  
44 Propensity score

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58 **INTRODUCTION**

59 Hospital-acquired infections (HAI) are a well-known source of morbidity in hospitalized  
60 patients but studies on attributable mortality have been confined to critically ill patients (1-7).  
61 The available literature suggests an increased mortality associated with HAIs, especially in  
62 patients with bloodstream infections or pneumonia, or in those with a surgical indication for  
63 admission (2-9). The association between death and HAI after cardiac surgery has been  
64 incompletely studied (10-21). Most studies focused on the identification of risk factors for  
65 HAI after cardiac surgery and concluded that HAI are directly related to patients'  
66 comorbidities, intraoperative factors, and postoperative management. A few studies assessed  
67 HAI attributable mortality, with confusing results, mostly due to potential confounders such  
68 as differences in baseline characteristics (for example comorbidities, age) or non evaluated  
69 risk-factors (for example type of surgery, length of cardiopulmonary bypass) or the method  
70 used for statistical analysis (for example multi state model, matched pair analysis) (10,13,17).  
71 Propensity score matching minimizes the influence of confounding factors, and is appropriate  
72 where only observational studies are feasible (6, 22). To our knowledge, this method has been  
73 used to estimate the attributable mortality of HAI in cardiac surgery patients only once, in a  
74 single center retrospective study that included only patients with a prolonged intensive-care-  
75 unit (ICU) stay. The authors concluded that HAI may increase death by 15 % (13).

76 We hypothesized that HAI after cardiac surgery are responsible for an increased mortality.  
77 Therefore we conducted an observational study with propensity-score matched analysis in  
78 order to assess the incidence, factors and outcomes associated with HAI in patients  
79 undergoing cardiac surgery. The primary objective was to determine the HAI-attributable  
80 mortality fraction. The secondary objective was to identify variables associated with death in  
81 patients with HAI after cardiac surgery.



82

## 83 MATERIAL AND METHODS

### 84 Setting and Patients

85 We conducted a retrospective analysis of prospectively collected data, in accordance with the  
86 Strengthening The Reporting of Observational Studies in Epidemiology (STROBE)  
87 guidelines. The study took place in a French cardiovascular and thoracic surgery ward in a  
88 1,500 bed tertiary university hospital. Prospective data were collected routinely for all patients  
89 undergoing cardiac surgery as part of an ongoing quality improvement program. All patients  
90 who underwent open cardiac surgery from the 1<sup>st</sup> of January 2012 to the 31<sup>th</sup> of December  
91 2018 were screened and only patients without missing data were finally included. Patients  
92 were followed from the day of surgery until death or discharge from the hospital (including  
93 care in the ICU and non-ICU wards). A dedicated research nurse followed patients from  
94 discharge until one year after surgery. In hospital, caregivers followed the recommendations  
95 of the French Society for Hospital Hygiene regarding the prevention and treatment of HAI  
96 (available at <https://sf2h.net>). As part of our institutional protocol, all patients were  
97 decolonized with intra-nasal mupirocine 2 days before surgery (23). Patients received 1.5g of  
98 intravenous cefuroxime at the beginning of the procedure, and then 750mg every two hours  
99 until the end of operation for surgical prophylaxis

100 Patients were informed of the prospective collection of the data and those who declined were  
101 excluded from the study. The local ethics committee (« comité d'éthique du CHU de  
102 Rennes ») approved the study (N°19.53).

103

104

105 **Definitions**

106 Based on previous publications which reported that the vast majority of HAI were due to  
107 hospital acquired bloodstream infection (BSI), hospital acquired pneumonia (HAP) and SSI,  
108 and because other HAI (such as urinary tract infections) have not been associated with an  
109 increased mortality, only BSI, HAP and SSI were included in this study (10-17). We  
110 considered HAI to be those diagnosed more than 48 hours after admission and which were not  
111 incubating on admission, per CDC guidelines (24, 25). BSI was defined as one positive blood  
112 culture, except for common skin contaminants (coagulase negative *Staphylococcus* species,  
113 *Corynebacterium* species, *Propionibacterium acnes* and *Micrococcus* species) where BSI  
114 required two positive blood cultures drawn on separate occasions.

115 The diagnosis of HAP included both ventilated and non-ventilated patients and was based on  
116 clinical signs (fever), radiographic findings (new infiltrate on chest-X-ray or CT scan), a  
117 positive microbiological culture of an endotracheal aspirate ( $\geq 10^6$  colony-forming units/mL)  
118 or a broncho-alveolar lavage ( $\geq 10^4$  colony-forming units/mL) and leukocytosis. Finally, SSI  
119 was defined by fever, clinical or radiographic evidence of wound infection (erythema,  
120 purulent drainage, wound dehiscence, rim-enhancing collections), and micro-organism(s)  
121 identified from the deep soft tissues. Only thoracic wound infections were considered, not  
122 peripheral SSIs such as at the site of vein harvest. Diagnosis of HAI was made by the treating  
123 physician, and independently confirmed by two study physicians who reviewed relevant  
124 imaging, microbiologic data, and medical records.

125 Baseline patient characteristics were collected on admission (age, sex, diagnostic category  
126 [planned versus emergency surgery], admission from another ICU, body mass index, chronic

127 kidney disease, chronic respiratory failure, cirrhosis, cancer, diabetes, hypertension, stroke,  
128 intubation before surgery). Other data were collected during surgery (circulatory arrest for  
129 surgery, duration of cardio-pulmonary bypass, transfusion of blood products) and during the  
130 hospital stay (number of days at risk for HAI, intubation for more than 48 hours, use of a  
131 ventricular assist device, catecholamine use after surgery, post-operative left ventricular  
132 dysfunction, stroke, reoperation). Definitions are available in the supplementary data. The  
133 number of days at risk for HAI was the number of days in the hospital from the 48<sup>th</sup> hour of  
134 stay until discharge or death (for patients without HAI) or until the first HAI occurrence (for  
135 patients with HAI). The day of HAI diagnosis was considered as the day of collection of the  
136 positive microbiological sample associated with the HAI.

137

### 138 **Primary and secondary endpoints**

139 The primary endpoint of the study was the attributable mortality fraction due to HAI after a  
140 cardiac operation. HAI attributable mortality fraction is the proportion of death due to HAI,  
141 or, in other words, the proportion of all death that might be prevented by eliminating HAI  
142 (26). This was calculated by comparing the difference in the number of deaths in patients who  
143 developed HAI with the number of deaths in a group of propensity-matched patients who did  
144 not develop HAI, (i.e. Attributable mortality = [number of hospital deaths among patients  
145 with HAI – number of hospital deaths among matched patient]/ number of hospital deaths in  
146 whole cohort). Secondary endpoints were the association between hospital death and  
147 microorganisms responsible for HAI or the sites of HAI (i.e. BSI, HAP, SSI).

148

149

**150 Statistical analysis**

151 Statistical analysis was performed with the statistical software R 3.4.3. Incidence and  
152 prevalence were expressed with the 95 percent confidence interval (95% CI). Categorical  
153 variables were expressed as number (percentage) and continuous variables as median and  
154 interquartile range [IQR]. When appropriate, the chi-square test and the Fisher's exact test  
155 were used to compare categorical variables. The Man-Whitney U test and Kruskal-Wallis  
156 tests were used for continuous variables when applicable. All tests were two-sided, and a P-  
157 value less than 0.05 was considered statistically significant.

158 The probability of developing a HAI was estimated using a multivariable logistic regression  
159 model that incorporated variables associated with HAI, while hazard of death was estimated  
160 with a multivariable cox regression model. Due to the high number of variables significantly  
161 associated either with death or with HAI, only variables with a p-value  $<0.05$  in the univariate  
162 analysis were included in the multivariable analysis. Then, to draw unbiased marginal  
163 estimates of exposure effect, a propensity-score matched analysis was performed. As potential  
164 confounders, we included for propensity-score matching all non-redundant variables  
165 independently associated with HAI (event) or death during hospital stay (outcome) with p-  
166 value  $\leq 0.05$  in the logistic regression (HAI) or cox-model (death) multivariable analysis.  
167 Using the MatchIt package, a k-nearest neighbor algorithm was used for propensity-score  
168 matching with a 1:1 ratio. Each patient with HAI was matched with 1 patient without HAI.

169 Multivariable competitive risk analysis was performed using the Fine-Gray model for the  
170 cumulative incidences of the competing events, namely discharge alive and death during  
171 hospital stay (27). The Fine-Gray model measures the association between HAI and outcome  
172 (death in Hospital) in which the competing event (discharge alive) actively contributes to  
173 modify the risk of the outcome. Therefore subdistribution Hazard Ratio (sdHR)  $>1$  indicates

174 that those with exposure (HAI) will be seen to have a quicker time to death. Conversely, a  
175  $sdHR < 1$  indicates a longer time before death for those exposed (27). Because HAI developed  
176 during survey and not at inclusion, we used a multistate model (28). Therefore, patients with  
177 HAI were included twice, first in the group without HAI during the period at risk of HAI, then  
178 they were censored from this group and were included in the HAI group only from HAI onset  
179 until discharge or death.

180 The analytic steps can be summarized as follows: first, patients with HAI were matched with  
181 similar patients without HAI based on their probability (propensity score calculation) to  
182 develop HAI and to die during hospital stay. Then, among patients with HAI and matched  
183 patients, we compared the association between HAI and death during hospital stay. Finally,  
184 excess of death (difference in the number of dead) in the HAI group was used to estimate HAI  
185 attributable mortality fraction in the full cohort.

## 186 **RESULTS**

### 187 **Population**

188 Of 8,969 admissions for cardiac surgery during the study period, 8,893 patients had a length  
189 of stay in hospital of 2 days or more and were therefore exposed to the risk of HAI. Of these,  
190 40 patients (0.4%) were excluded due to missing data, leaving a study cohort of 8,853 patients  
191 (supplementary Figure 1). Median age was 69 years [61–77] and the most common  
192 comorbidity was hypertension, which affected 4,893 patients (55.3%). Predicted mortality  
193 based on EUROSCORE II was 2.3%. The majority of operations were elective (87.2%),  
194 cardiopulmonary bypass lasted for 74 minutes [55–106] and only 1,589 patients (17.9%)  
195 received homologous red-blood cells during their operation. The median length of hospital  
196 stay was 10 days [8–14] and 211 patients (2.4%) died during hospital stay (Table 1).

**197 Incidence and risk factors for hospital acquired infection**

198 Of 8,853 patients with a length of stay of 2 days or more, 370 (4.2%) acquired a total of 500  
199 infections during their stay: 110 had one or more BSI (1.2%), 161 had one or more HAP  
200 (1.8%) and 173 had one or more SSI (2.0%). The 500 infections occurred over a total of  
201 118,424 days of hospitalization, therefore the HAI incidence density rate was 4.2 HAI per  
202 1,000 patient-days. Factors independently associated with HAI were assessed with a logistic-  
203 regression model. Among pre-operative variables, BMI>30 kg/m<sup>2</sup> (Odd Ratio [OR] = 1.55;  
204 95% CI [1.20–2.00] p <0.001), chronic renal failure (OR = 1.66; 95% CI [1.13–2.45] p  
205 =0.009), chronic respiratory failure (OR = 1.65; 95% CI [1.17–2.35] p =0.005) and diabetes  
206 (OR = 1.43; 95% CI [1.08–1.89] p =0.006) were independently associated with HAI. Five  
207 surgical factors were independently associated with HAI: valve replacement (OR = 0.58; 95%  
208 CI [0.44–0.77]; p <0.001), combined operations (OR = 1.64; 95% CI [1.15–2.33]; p <0.001)  
209 emergency operations (OR = 1.77; 95% CI [1.33–2.33]; p <0.001), CPB length > 100 min  
210 (OR = 1.68; 95% CI [1.28–2.19] p <0.001) and platelet transfusion (OR = 1.58; 95% CI  
211 [1.09–2.29] p =0.016). Finally, post-operative variables associated with HAI were intubation  
212 > 48 hours after cardiac operation (OR = 6.89; 95% CI [4.70–10.09] p <0.001), reoperation  
213 (OR = 3.13; 95% CI [2.39–4.11] p <0.001), left ventricular ejection fraction < 50% (OR =  
214 1.35; 95% CI [1.05–1.74] p =0.018) and stroke (OR = 2.22; 95% CI [1.18–4.17] p =0.013)  
215 (Table 2).

**216 Hazard ratio for death during hospital stay**

217 Variables associated with death were evaluated using a cox-model regression. Several  
218 variables were identified. With cox model regression analysis, HAI was still independently  
219 associated with death during hospital stay (HR = 4.39; 95% CI [3.06–6.30]; p <0.001) (Table  
220 3). A sub-group analysis was performed with respect to type of surgery. Among the 5,441

221 patients with valve surgery, HAI was independently associated with death during hospital stay  
222 (sdHR 4.08 [2.78-5.99]  $p < 0.001$ ). Similarly, among the 3,468 patients who underwent  
223 coronary artery bypass grafting (CABG), HAI was also independently associated with death  
224 during hospital stay (sdHR 4.56 [2.59-8.04]  $p < 0.001$ ). Because SSI was not associated with  
225 death in the whole population, a not previously specified analysis was performed in the 3,468  
226 patients who underwent CABG. Of these patients 101 (2.9%) developed a SSI, of whom 6  
227 died (5.9%). Of the 3367 patients without SSI, 53 patients died (1.6%). When a multivariable  
228 Fine-Gray analysis was performed, SSI was independently associated with death in Hospital  
229 (sdHR=2.94; 95% CI [1.39-6.22];  $p = 0.005$ ).

230

### 231 **Hospital-acquired infection attributable mortality fraction with propensity-score** 232 **matched analysis**

233 For propensity score matching, every variable independently associated with HAI or death  
234 during hospital stay was included in the analysis. Based on these results, the 370 patients with  
235 HAI were matched with 370 patients without HAI (supplementary Figure 2). Baseline  
236 characteristics of the 2 groups are reported in Table 1 and were fully balanced, as was  
237 predicted mortality with EUROSCORE II ( $p = 0.90$ ). When a cumulative risk analysis with  
238 discharge and death as competing variables (Fine and Gray) was performed in this dataset,  
239 patients with HAI had a higher risk for death (sdHR = 5.39; 95% CI [3.70-7.86];  $p < 0.001$ ).  
240 Among patients with HAI 57 patients died during hospital stay (15.4%), compared with 21  
241 patients without HAI (5.7%,  $p < 0.001$ ) (supplementary Figure 3). Based on these results, the  
242 number needed to harm was 10 [7-19] (i.e. there was 1 supplementary death per 10 patients  
243 exposed to HAI). Since there were 36 excess deaths in the HAI group, the attributable  
244 mortality fraction of HAI in the overall population was 17.1 % [12.3% – 22.8%] (i.e. 17.1%

245 of the hospital deaths after cardiac operations were related to HAI). Similarly, among patients  
246 with HAI, more deaths were observed (57 patients, 15.4%) than were predicted by  
247 EUROSCORE II (16 patients, 4.3%) ( $p < 0.001$ ).

#### 248 **Outcomes of patients with hospital-acquired infection by microorganism**

249 Of the 370 patients with HAI and 370 propensity-score matched patients, *Pseudomonas*  
250 *aeruginosa* was the only HAI microorganism associated with an increased risk of hospital  
251 death after adjustment for site of infection with a Fine-Gray model (sdHR = 2.09; 95% CI  
252 [1.23-3.49];  $p = 0.005$ ) (Figures 1 and 2). Microorganisms responsible for HAI are reported by  
253 site of HAI in Table 4.

#### 254 **Outcomes of patients with hospital-acquired infection by site of infection**

255 Conversely, after adjustment for microorganisms responsible for HAI with Fine-Gray model,  
256 bloodstream site of infection (sdHR = 2.08; 95% CI [1.19–3.63]  $p = 0.010$ ) and pneumonia  
257 (sdHR = 1.68; 95% CI [1.02–2.77];  $p = 0.04$ ) were independently associated with an  
258 increased hazard for death during hospital stay (Figure 1 and 2).

259

## 260 **DISCUSSION**

261 This study demonstrated that while hospital acquired infections were a relatively uncommon  
262 complication after cardiac operations, they were responsible for approximately one sixth of  
263 hospital deaths. This increased post-operative mortality was observed with both cox  
264 regression model, and when comparing patients with HAI to propensity-score matched  
265 patients without HAI using a Fine-Gray model. The relatively low rate of HAI observed in  
266 this study was in line with previous studies of HAI in a cardiac surgery setting (11-14). This



267 study confirmed the previously described association between HAI and death (13, 17, 19-21)  
268 but is, to our knowledge, the first estimation of HAI-attributable mortality fraction in a large  
269 cohort of patients who underwent cardiac operations.

270 Attributable mortality of ICU-acquired infection has been widely studied in both medical and  
271 surgical ICUs (1-9). Although association between ventilator-associated pneumonia (VAP)  
272 and death remains controversial in medical patients, other studies have provided evidence of  
273 such an association in surgical patients (7, 9). In a large meta-analysis of randomized trials of  
274 VAP prevention involving 6,284 patients, Melsen et al. estimated a VAP attributable  
275 mortality of 69 % in surgical patients, compared with 0% for medical patients (9). Similar  
276 results were found in a large French prospective study including 2,873 mechanically  
277 ventilated patients, with an attributable mortality of approximately 10% in surgical patients  
278 compared with no attributable mortality in medical patients (7).

279 Patients undergoing cardiac operations differ notably from patients admitted in other surgical  
280 ICUs due to exposure to CPB. Exposure of the patients' blood to the non-endothelialised  
281 surface of the circuit results in the widespread activation of the innate immune system that  
282 may modify the response to secondary infection (29, 30). Prior studies have demonstrated that  
283 patients exposed to extra-corporal circulation are at increased risk of colonization and  
284 secondary infection with multidrug resistant bacteria and that these infections are associated  
285 with increased mortality (31, 32). Further studies are needed in order to clarify the  
286 pathophysiology of HAI after CPB.

287 Among the cardiac surgery patients in this study, both bloodstream infections and pneumonia  
288 were associated with increased in-hospital mortality, but there was no association between  
289 SSI and mortality. These findings differ from a previous study where Mazeffi et al. reported  
290 that SSI and BSI were associated with mortality in cardiac surgery patients with prolonged

291 ICU stays, whereas pneumonia was not (13). This difference may be explained by differences  
292 in the patient population. Mazeffi et al. including only patients with prolonged ICU stays,  
293 while this study included all patients who underwent cardiac operations. Others studies  
294 supported an increased risk for death in patients with BSI or pneumonia (19, 20) and in  
295 patients with SSI (13, 16). As our findings concerning the association between SSI and  
296 mortality differ from prior published work, we performed a not pre-specified analysis among  
297 patient with CABG operations, who are known to be at higher risk for SSI (16). In this  
298 subgroup of patients, SSI was associated with increased in-hospital mortality, suggesting that  
299 a difference in patient populations may account for this finding.

300

301 Among micro-organisms responsible for HAI, *Pseudomonas aeruginosa* is one of the most  
302 common gram-negative pathogens and has been responsible for well-documented ICU  
303 epidemics (33-36). Compared with other microorganisms, including non-fermenting gram-  
304 negative bacilli, *Pseudomonas aeruginosa* has been associated with an increased morbidity  
305 and mortality in our study, as in previous publications (2, 35, 36). Assessing excess mortality  
306 and length of stay in ICU in patients with BSI or pneumonia, Lambert et al. found that  
307 infection due to *Pseudomonas aeruginosa* reduced hazard ratio for ICU discharge. The  
308 authors concluded that this microorganism carried the highest burden of health-care-  
309 associated infections because of its high prevalence and pathogenicity (2). We observed  
310 similar results in our study, as only *Pseudomonas aeruginosa* infections were associated with  
311 death among patients with HAI and propensity-score match patients. Other authors report  
312 similar result, with a higher attributable mortality for BSI due to Gram-negative bacteria than  
313 to other microorganisms (19). However, they did not separately analyze the influence of  
314 *Pseudomonas aeruginosa* versus other Gram-negative bacteria.

315 The main strengths of our study are the large patient population and the use of propensity-  
316 matching to reduce the impact of potential confounders (6, 19). While the nature of hospital-  
317 acquired infections requires an observational study design, the propensity score matching in  
318 this study was highly effective and measured characteristics of patients with HAI and  
319 propensity-score matched patients were well balanced. In addition, we were able to account  
320 for the competing event nature of the main outcome.

321 Our study has also several limitations. First, the time dependency of mortality on HAI was not  
322 extensively studied as we could not obtain patient-related variables specific to the day of HAI  
323 (for example sequential organ failure assessment score or use of epinephrine on the day of  
324 HAI). Such data would have reduced time-dependent bias. Moreover, relative risk of HAI  
325 could differ during hospital stay with a higher risk of HAI in the ICU than in other wards.  
326 Although a multistate model took into account the length of stay before HAI occurrence, we  
327 could not distinguish length of stay in the ICU from length of stay in another ward. Therefore,  
328 although we performed a multivariable analysis and case-control matching to reduce time  
329 dependency bias time dependency may still be considered a potential confounder. Second, we  
330 did not have data regarding antimicrobial susceptibility or the appropriateness of  
331 antimicrobial agents used for HAI treatment. However, prior studies have reported that the  
332 additional effect of antimicrobial resistance patterns on attributable mortality is comparatively  
333 low (2). Third, due to missing data, we did not control for some other residual confounders  
334 such as glucose control, steroid administration, immunosuppression, or obesity/malnutrition.  
335 Fourth, the diagnosis of HAI was made by the treating physician. Although HAI diagnosis  
336 was independently confirmed by two study physicians, this remains a limitation. This is  
337 particularly true for the diagnosis of pneumonia, which was made using a set of clinical  
338 criteria described above, though less of an issue for SSI and BSI where diagnosis relied on

339 documented culture data. Finally, this was a retrospective single center study, limiting its  
340 external generalizability.

341

## 342 **CONCLUSION**

343 In this large prospective observational study, HAI after cardiac surgery was associated with  
344 an increased risk for death especially for BSI and pneumonia or when *Pseudomonas*  
345 *aeruginosa* was involved. The fraction of mortality attributable to HAI was 17.1 %. This  
346 result can be used as a benchmark in order to evaluate strategies that aim to reduce HAI  
347 incidence and attributable mortality fraction in cardiac surgery setting.

348

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## 351 **Declarations of interest**

352 None.

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501

## 502 **Figure legends**

503 Figure 1

504 Subdistribution Hazard ratios (sdHR) for hospital death among 370 cardiac surgery patients  
505 with hospital acquired infection (HAI) and 370 propensity score-matched patients without  
506 HAI. Competitive risk analysis was performed with a Fine-Gray method with discharge and  
507 death being competing outcomes. Diamonds correspond to the estimated sdHR and bars  
508 delimit 95% confidence intervals. For subgroup analysis, patients exposed to a risk (for  
509 example pneumonia) were compared to all other patients in the cohort without exposure (all  
510 patients without pneumonia among those with a HAI and the 370 matched patients).

511 \* Subgroup analysis by site of infection was adjusted for micro-organism

512 \*\* Subgroup analysis by microorganism was adjusted for site of infection

513 Figure 2: Graphical abstract: Mortality attributable to hospital-acquired infections (HAI) after  
514 cardiac surgery and subdistribution Hazard Ratios (sdHR) for hospital death for the following  
515 sub groups: Pneumonia, Bacteremia and *Pseudomonas Aeruginosa* infections

516 Video 1: Mortality attributable to hospital-acquired infections after cardiac surgery: Nicolas  
517 Nesslerer presents the findings and implications of the study.

518

Table 1: Baseline characteristics and outcomes of study patients.

Variables	All patients		Patients with HAI		Propensity-score matched patients		p-value*	Standardized Difference*
	n = 8854		n = 370		n = 370			
Age, year [IQR]	69	[61-77]	68	[59-75]	68	[59-75]	0.98	0.060
Body mass index, [IQR]	26.3	[23.7-29.3]	26.8	[24.4-30.3]	26.8	[23.6-30.5]	0.54	0.013
Male – no. (%)	6491	(73.3)	285	(77.0)	293	(79.2)	0.48	0.021
Euroscore II predicted mortality, – % mean (SD)	2.4	(3.4)	4.3	(6.4)	4.2	(6.3)	0.90	
<i>Comorbidities</i>								
Chronic kidney failure – no. (%)	428	(4.8)	40	(10.9)	43	(11.6)	0.82	0.008
Chronic respiratory failure – no. (%)	663	(7.5)	43	(11.6)	37	(10.0)	0.55	0.016
Cirrhosis – no. (%)	53	(0.6)	2	(0.5)	0	(0.0)	0.48	0.005
Cancer – no. (%)	662	(7.5)	32	(8.6)	25	(6.7)	0.41	0.002
Diabetes – no. (%)	1411	(15.9)	83	(22.4)	94	(25.4)	0.39	0.030
Hypertension – no. (%)	4893	(55.3)	200	(54.1)	219	(59.2)	0.18	
Stroke – no. (%)	188	(2.1)	8	(2.2)	13	(3.5)	0.37	
<i>Pre-surgery</i>								
Intubation – no. (%)	21	(0.3)	4	(1.1)	2	(5.4)	0.68	
Admission from another ICU – no. (%)	38	(0.5)	4	(1.1)	4	(1.1)	1	0.001
<i>Surgery</i>								
Valve – no. (%)	5441	(61.5)	189	(51.1)	202	(54.6)	0.42	0.035
Coronary artery by-pass – no. (%)	3468	(39.2)	160	(43.2)	161	(43.5)	1	0.002
Combined – no. (%)	910	(10.3)	57	(15.4)	58	(15.7)	0.94	0.005
Other – no. (%)	858	(9.7)	78	(21.1)	65	(17.6)	0.33	
Emergency surgery – no. (%)	1136	(12.8)	113	(30.5)	121	(32.7)	0.58	0.022
Circulatory arrest – no. (%)	370	(4.2)	29	(7.8)	41	(11.1)	0.17	
Length of CPB, minutes [IQR]	74	[55-106]	100	[64-145]	105	[69-145]	0.54	0.043
Red-blood cell transfusion – no. (%)	1589	(17.9)	110	(29.7)	114	(30.8)	0.81	0.011
Platelet transfusion – no. (%)	547	(6.2)	65	(17.6)	71	(19.2)	0.64	0.016
<i>Post-operative events</i>								
Intubation for > 48 hours – no. (%)	178	(2.0)	58	(15.7)	47	(12.7)	0.29	0.030
Stroke – no. (%)	155	(1.8)	18	(4.8)	15	(4.1)	0.86	0.005
Left ventricular ejection – % [IQR]	61	[55-65]	60	[45-65]	60	[45-65]	0.26	0.002
Reoperation – no. (%)	807	(9.1)	109	(29.5)	112	(30.3)	0.87	0.008
Ventricular assist device – no. (%)	466	(5.3)	60	(16.2)	61	(16.0)	1	0.003
<i>Outcome</i>								
Length of stay in hospital, days [IQR]	10	[8-14]	24	[11-40]	13	[9-22]	<0.001	
Death during hospital stays – no. (%)	211	(2.4)	57	(15.4)	21	(5.7)	<0.001	
Death at day 90 – no. (%)	261	(2.9)	74	(20.0)	28	(7.6)	<0.001	

Note. HAI: Hospital-acquired infection. IQR: Inter-quartile ranges. SD: Standardized derivation. ICU : intensive care unit. CPB : cardio-pulmonary bypass. \* For comparison between patients with HAI and matched patients.

Table 2: Risk factors for hospital-acquired infection.

	Univariate analysis			Multivariable analysis		
	OR	95% CI	p-value	OR	95% CI	p-value
Age, per supplementary year	0.99	0.98-1.00	0.009	1.00	0.99-1.01	0.79
Body mass index > 30 kg/m <sup>2</sup>	1.42	1.12-1.80	0.033	1.55	1.20-2.00	<0.001
Male	1.23	0.96-1.57	0.10			
Chronic kidney failure	2.53	1.79-3.57	<0.001	1.66	1.13-2.45	0.009
Chronic respiratory failure	1.71	1.24-2.36	0.001	1.65	1.17-2.35	0.005
Cirrhosis	0.88	0.22-3.71	0.85			
Cancer	1.67	1.20-2.32	0.002	1.20	0.81-1.77	0.37
Diabetes	1.56	1.21-2.00	0.005	1.43	1.08-1.89	0.006
Hypertension	0.95	0.77-1.17	0.63			
Stroke history	1.02	0.50-2.09	0.96			
Intubation before surgery	5.44	1.82-16.26	0.002	1.89	0.56-6.34	0.31
Admission from another ICU	2.71	0.96-7.69	0.060			
Valve	0.64	0.52-0.79	<0.001	0.58	0.44-0.77	<0.001
Coronary artery by-pass	1.19	0.97-1.47	0.10			
Combined	1.59	1.15-2.14	0.002	1.64	1.15-2.33	0.006
Other	2.64	2.04-3.43	<0.001	0.95	0.65-1.39	0.79
Emergency surgery	3.20	2.55-4.04	<0.001	1.77	1.33-2.36	<0.001
Circulatory arrest for surgery	2.05	1.39-3.02	<0.001	0.68	0.41-1.13	0.14
Length of CPB >100 minutes	2.67	2.17-3.30	<0.001	1.68	1.28-2.19	<0.001
Red-blood cell transfusion during surgery	2.00	1.59-2.52	<0.001	1.06	0.80-1.40	0.71
Platelet transfusion during surgery	3.54	2.67-4.70	<0.001	1.58	1.09-2.29	0.016
Intubation for > 48 hours after surgery	13.41	9.59-18.74	<0.001	6.89	4.70-10.09	<0.001
Stroke after surgery	4.87	2.86-8.30	<0.001	2.22	1.18-4.17	0.013
Left ventricular ejection < 50% after surgery	2.17	1.75-2.71	<0.001	1.35	1.05-1.74	0.018
Ventricular assist device after surgery	3.85	2.87-5.17	<0.001	1.34	0.93-1.95	0.12
Reoperation during hospitalization	4.66	3.68-5.90	<0.001	3.13	2.39-4.11	<0.001
Length of exposure to the risk, per supplementary days	1.01	1.00-1.01	0.002	1.00	0.99-1.01	0.95

Note. ICU : intensive care unit. CPB : cardio-pulmonary by pass.

Table 3 : Hazard ratio for death during hospital stay.

	Univariate analysis			Multivariable analysis		
	HR	95% CI	p-value	HR	95% CI	p-value
Age. per supplementary year	1.02	1-1.03	0.016	1.05	1.03-1.07	<0.001
Body mass index > 30 kg/m <sup>2</sup>	0.82	0.57-1.18	0.289			
Male	0.57	0.43-0.76	<0.001	0.57	0.42-0.77	<0.001
Chronic kidney failure	3.12	2.08-4.68	<0.001	1.68	1.1-2.57	0.016
Chronic respiratory failure	1.76	1.16-2.68	0.008	1.59	1.04-2.44	0.034
Cirrhosis	5.29	2.35-11.91	<0.001	4.72	2.02-11.03	<0.001
Cancer	1.69	1.1-2.59	0.016	1.56	1.01-2.41	0.043
Diabetes	1.4	1-1.97	0.052			
Hypertension	0.98	0.74-1.29	0.89			
Stroke history	1.93	0.95-3.92	0.068			
Intubation before surgery	6.86	2.2-21.46	0.001	1.1	0.33-3.63	0.88
Admission from another ICU	7.5	3.33-16.91	<0.001	4.05	1.7-9.64	0.002
Valve	0.99	0.75-1.31	0.943			
Coronary artery by-pass	0.64	0.47-0.87	0.004	0.77	0.49-1.2	0.25
Combined	1.66	1.14-2.43	0.008	1.46	0.84-2.54	0.18
Other	3.31	2.41-4.53	<0.001	1.35	0.9-2.02	0.15
Emergency surgery	4.41	3.32-5.86	<0.001	2.1	1.46-3.02	<0.001
Circulatory arrest for surgery	2.44	1.52-3.92	<0.001	0.7	0.4-1.22	0.21
Length of CPB >100 minutes	3.8	2.87-5.04	<0.001	1.91	1.33-2.72	<0.001
Red-blood cell transfusion during surgery	4.19	3.18-5.53	<0.001	1.47	1.05-2.04	0.023
Platelet transfusion during surgery	5.07	3.68-7	<0.001	1.36	0.92-2.03	0.12
Intubation for > 48 hours after surgery	8.76	5.91-12.99	<0.001	1.61	1.01-2.55	0.043
Stroke after surgery	6.88	4-11.84	<0.001	2.57	1.44-4.59	0.001
Left ventricular ejection < 50% after surgery	2.57	1.94-3.41	<0.001	1.54	1.12-2.12	0.009
Ventricular assist device after surgery	7.56	5.57-10.28	<0.001	2.9	1.99-4.23	<0.001
Reoperation during hospitalization	3.64	2.66-4.98	<0.001	1.45	1.01-2.08	0.045
<i>Hospital-acquired infection</i>						
Any	9.87	7.26-13.41	<0.001	4.39	3.06-6.3	<0.001
Bloodstream infection	13.44	8.90-20.29	<0.001	3.98	2.46-6.44	<0.001
Pneumonia	14.83	10.42-21.11	<0.001	4.54	3.00-6.87	<0.001
Surgical-site infection	2.69	1.43-5.08	<0.001	1.59	0.82-3.09	0.17

Note. ICU : intensive care unit. CPB : cardio-pulmonary by pass.

Table 4. Microorganisms responsible for Hospital-acquired infection.

Microorganisms	All isolates		Bloodstream infection		Pneumonia		Surgical site infection	
	n	(%)	n	(%)	n	(%)	n	(%)
<i>Staphylococcus-aureus</i>	143	(23.7)	72	(38.5)	24	(9.9)	47	(27.0)
Coagulase-negatives <i>Staphylococci</i>	114	(18.9)	38	(20.3)	6	(2.5)	70	(40.2)
<i>Enterococcus sp.</i>	18	(3.0)	9	(4.8)	3	(1.2)	6	(3.4)
<i>Streptococcus sp.</i>	30	(5.0)	8	(4.3)	19	(7.8)	3	(1.7)
<i>Pseudomonas aeruginosa</i>	95	(15.7)	23	(12.3)	66	(27.1)	6	(3.4)
<i>Enterobacteriaceae</i>	114	(18.9)	27	(14.4)	58	(23.8)	29	(16.7)
<i>Anaerobes</i>	10	(1.7)	5	(2.7)	0	(0)	5	(2.9)
<i>Others</i> Gram-negative bacilli *	47	(7.8)	1	(0.5)	45	(18.5)	1	(0.6)
<i>Candida sp.</i>	3	(0.5)	2	(1.1)	0	(0)	1	(0.6)
<i>Others**</i>	30	(5.0)	2	(1.1)	22	(9.1)	6	(3.4)
Total	604	(100)	187	(100)	243	(100)	174	(100)

\* Included *Haemophilus sp.*, *Pasteurella sp.* and *Stenotrophomonas sp.*

\*\* Included *Moraxella sp.*, *Neisseria sp.* and *Corynebacterium sp.*



## Mortality attributable to hospital-acquired infections after cardiac surgery



8,853 patients



Cardiac surgery



2012-2019

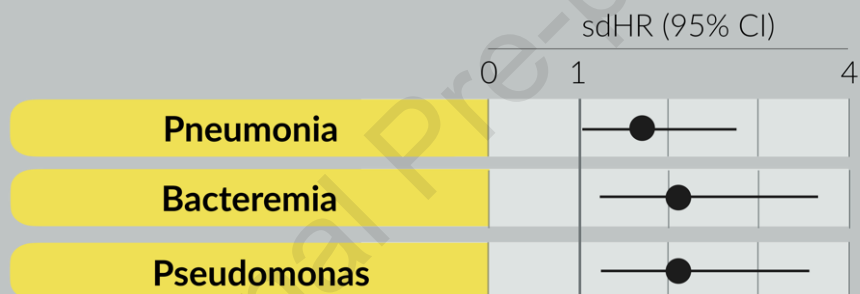
**Postoperative infections**

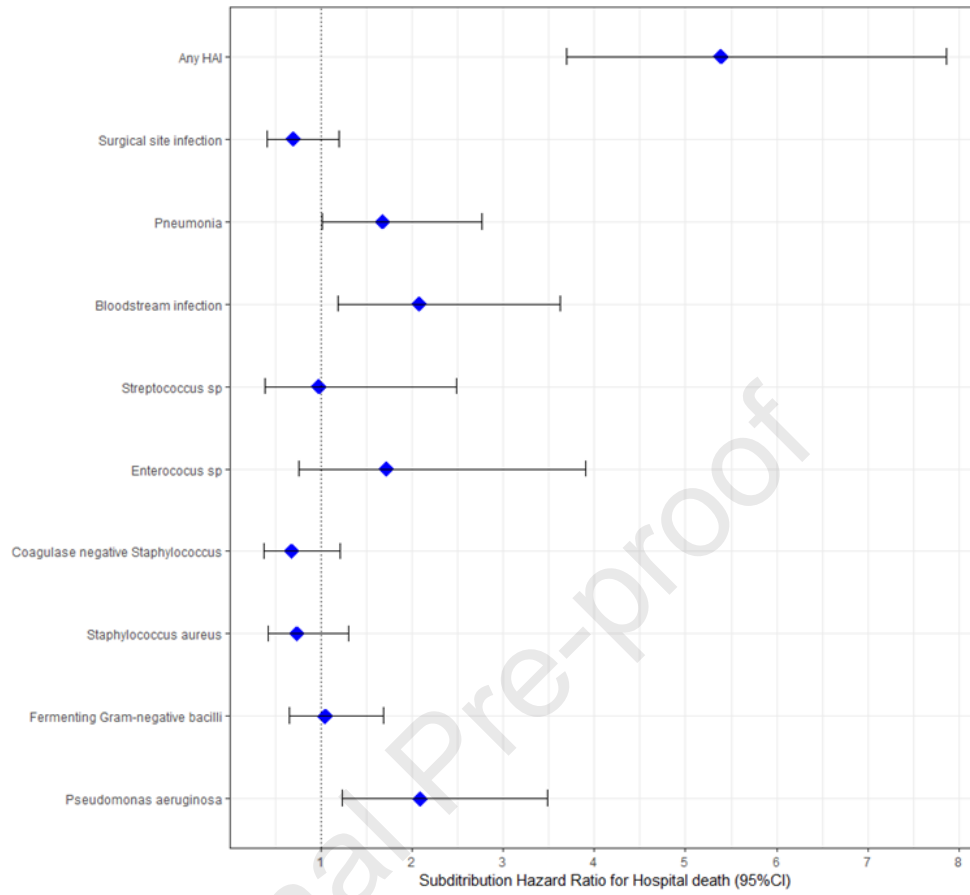
4 %

**Attributable mortality**

17 %

### In hospital mortality in patients with hospital-acquired

**Low incidence but major impact on postoperative mortality**



## Mortality attributable to hospital-acquired infections after cardiac surgery



8,853 patients



Cardiac surgery



2012-2019

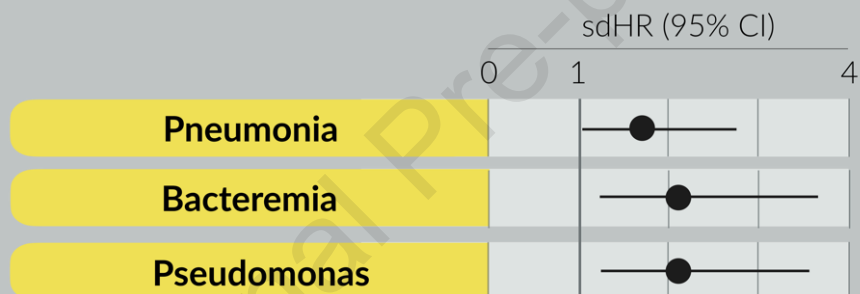
**Postoperative infections**

4 %

**Attributable mortality**

17 %

### In hospital mortality in patients with hospital-acquired

**Low incidence but major impact on postoperative mortality**