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1 **Risk factors for surgical site infection after pancreatic surgery. A better postoperative**
2 **antibiotic strategy is possible.**

3 Running title: Can we reduce antibiotics exposure after pancreatic surgery?

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25

1 **Abstract:**

2 *Introduction:*

3 Pancreatic surgery is associated with high morbidity, mostly due to infectious complications,
4 so many centres introduce postoperative antibiotics for all patients. However, antibiotic
5 regimens vary according to local practices. The aims of this study were to describe the
6 occurrence of surgical site infection (SSI) and antibiotic prescription after pancreatic surgery,
7 and to determine the risk factors of postoperative SSI, in order to better define the clinical
8 indications for the prescription of antibiotics in this context.

9 *Patients and methods:*

10 All patients undergoing scheduled major pancreatic surgery from January 2007 to November
11 2018 were retrospectively included in the study. Patients were classified in four groups
12 according to SSI and routine postoperative antibiotic (ATB_{po}) prescription as follows:
13 SSI+/ATB_{po}+; SSI-/ATB_{po}+; SSI+/ATB_{po}-, SSI-/ATB_{po}-. In addition, risk factors (fever and
14 preoperative biliary prosthesis) associated with the occurrence of SSI and with antibiotic
15 prescription were analyzed using a logistic regression model.

16 *Results:*

17 Data from 149 patients (115 pancreaticoduodenectomies and 34 splenopancreatectomies)
18 were analyzed. Thirty patients (20.1%) experienced SSI and 42 (28.2%) received
19 postoperative antibiotics. We found no difference in routine postoperative antibiotic
20 prescriptions (26.7% versus 28.6%, p=0.9) between patients with and without SSI. Amongst
21 the 107 patients who were not routinely prescribed antibiotics postoperatively, 85 (79.4%) did
22 not develop an SSI. In-hospital mortality did not differ between infected and non-infected
23 patients (7% versus 2%, p=0.13). Postoperative fever was different between SSI+ and SSI-

1 (73.3% versus 34.2%, $p < 0.001$), while the prevalence of preoperative biliary prosthesis was
2 similar (37.9% versus 26.7%, $p = 0.3$).

3 *Conclusion:*

4 Non-routine antibiotic prescription after major pancreatic surgery allowed us to appropriately
5 spare antibiotics in 85 (56%) patients. This suggests that routine postoperative antibiotic
6 prescription could be excessive, but further studies are needed to confirm such antibiotic
7 stewardship. Fever appears to be a relevant clinical sign for individual-based prescription,
8 whereas the presence of a biliary prosthesis does not.

9

10 *Keywords: Major pancreatic surgery, pancreaticoduodenectomy, surgical site infection,*
11 *postoperative antibiotics, antimicrobial stewardship.*

1 **Introduction**

2 The high incidence of postoperative complications after pancreatic surgery [1, 2] has led
3 many teams to routinely prescribe postoperative antibiotics after pancreaticoduodenectomy
4 (PD) [3, 4]. This approach is not universal; some authors suggest that prophylactic antibiotic
5 prescription can be limited to the first 24 hours postoperatively [5], while others recommend
6 routine longer term use of antibiotics, especially in high-risk patients [3], or when surgery is
7 preceded by preoperative biliary drainage [4]. Indeed, preoperative bile duct drainage is
8 associated with increased infectious morbidity and a higher mortality rate in PD [6, 7]. This
9 may be related to increased difficulties in bile duct dissection during PD [1]. However, the
10 systematic use of postoperative antibiotics exposes patients to the emergence of multidrug-
11 resistant organisms (MDRO) or to potentially severe side effects of antimicrobial therapies.

12 The aim of the present study was to describe the occurrence of surgical site infection (SSI)
13 and routine postoperative antibiotic prescription after pancreatic surgery. Risk factors for SSI
14 were sought in order to identify patients in whom routine prescription of antibiotics could be
15 avoided.

16

17 **Patients and methods**

18 *Study design and data collection*

19 We conducted a single-centre observational, retrospective study in the university hospital
20 Ambroise Paré, Boulogne-Billancourt, France. All patients undergoing scheduled major
21 pancreatic surgery from January 2007 to November 2018 were included. During this period,
22 they were all admitted to the intensive care unit after surgery.

23 Patients who underwent emergency pancreatic surgery for acute pancreatitis or pancreatic
24 trauma were excluded, as were patients admitted preoperatively for sepsis or septic shock [8].

25 Patients were initially selected from the medical information database of the hospital under

1 the supervision of the medical information department using the following encoding
2 according to the 10th International Classification of Diseases: malignant pancreatic tumor and
3 malignant pancreatic neuroendocrine tumor (C25), malignant duodenal tumor (C17),
4 malignant bile duct tumor (C24), benign pancreatic tumor (D13.6), benign pancreatic
5 neuroendocrine tumor (D13.7) and other diseases of the pancreas (K86). Handwritten and
6 computerized (Orbis[®], Agfa Healthcare, Mortsels, Belgium) medical records were collected.
7 By chart review, the following data were extracted: age, gender, body mass index, significant
8 medical history (diabetes mellitus, chronic arterial disease, chronic heart failure, chronic
9 obstructive pulmonary disease and chronic kidney disease). We recorded severity scores at
10 day-1 (Sequential Organ Failure Assessment [SOFA] score [9] and the Simplified Acute
11 Physiology Score [SAPSII] [10], the kind of surgery, preoperative biliary instrumentation
12 and/or drainage with or without a bile duct prosthesis, antibiotic treatment during the three
13 months before surgery, preoperative bilirubin level, and data about postoperative process such
14 as the need for organ replacement therapy (mechanical ventilation, renal replacement therapy,
15 vasopressors), the occurrence of fever, the postoperative bilirubin level, MDRO acquisition,
16 the duration of hospital stay and mortality.

17 *Surgical procedure*

18 PD without pylorus preservation, also named the Whipple procedure [11], was performed
19 with pancreaticogastrostomy. The abdominal cavity was routinely drained with a Blake
20 multichannel silicone tube located in front of the biliary anastomosis and
21 pancreaticogastrostomy. A nasogastric tube was positioned by the surgeon in order to avoid
22 gastric distension and to monitor the pancreaticogastrostomy and the gastrojejunal
23 anastomosis. Distal pancreatectomy associated with splenectomy (DPS) was performed by
24 laparotomy. A Blake multichannel silicone tube was positioned in front of the front section of
25 the pancreas. Bile samples from the common bile duct were collected for microbiological

1 culture at the discretion of the surgeon. Biliary prostheses, if any, were sent for
2 microbiological analysis. The anaesthetic treatment was locally standardized and patients
3 were fitted with a jugular central venous catheter and a radial arterial catheter. Postoperative
4 analgesia mostly relied on patient-controlled epidural analgesia. Antibiotic prophylaxis
5 followed the local protocol [12, 13] with an infusion of 2 g of cefuroxime before incision and
6 a further 1 g every two hours if needed. Postoperative antibiotic treatment was not
7 protocolized and not systematically introduced and was determined on a case-by-case basis by
8 surgeons and anaesthetists at the time of surgery, depending on peri-operative observations
9 (e.g. purulent bile, presence of prosthesis, known preoperative colonized bile, peri-operative
10 fever) Post-discharge surveillance was performed by the surgical team, monthly for the first
11 six months and then adjusted for each patient/clinical situation (neoplasia or not, kind of
12 neoplasia, tumour classification)

13 *Definitions*

14 The main postoperative infectious complications, classified as SSI, pneumonia and
15 bacteremia, were collected in a 90-day timeframe after the surgery. SSI was diagnosed
16 according to the guidelines [14] as bacteriologically positive cultures associated with clinical
17 symptoms suggestive of infection. Given that superficial incisional SSI usually does not
18 require antibiotics, we decided to consider major deep incisional and organ/space SSI [14]
19 graded as Clavien-Dindo classification III or above, i.e. SSI requiring surgical, endoscopic or
20 radiological intervention (grade III) or life-threatening SSI (grade IV) [15]. A positive bile
21 culture without sign of infection and without antibiotics was not considered as SSI. Wound
22 infection defined as the presence of pus requiring wound opening and local treatment were
23 not considered as major SSI. SSI included intra-abdominal abscesses defined as postoperative
24 collection of infected liquid requiring puncture or drainage and the occurrence of tertiary
25 peritonitis (abdominal contracture associated with sepsis) requiring surgical intervention

1 under general anesthesia for abdominal cavity scrubbing and drainage. The diagnosis of
2 postoperative nosocomial pneumonia followed international guidelines [16]. Postoperative
3 bacteraemia was defined as one or more positive blood culture with pathogenic bacteria.
4 Systematic postoperative antibiotic prescription (ATB_{po}) was defined as antibiotics routinely
5 introduced immediately after surgery for at least 48 hours, in order to distinguish from
6 antibiotics that could have been prescribed for prophylaxis, which is not recommended to
7 exceed 24 hours [13, 17].

8 *Outcomes*

9 The main outcome was the occurrence of SSI within 90 days after surgery. The secondary
10 outcomes included postoperative prescription of antibiotics and vital status at hospital
11 discharge.

12 *Ethics*

13 The present study was approved by the ethics committee of the French Society of Anesthesia
14 and Intensive Care Medicine (SFAR n° IRB 00010254-2018-193).

15 *Statistical analysis*

16 Patients included in the study were classified in four groups according to the occurrence of
17 SSI and ATB_{po} as follows: SSI+/ATB_{po}+, SSI-/ATB_{po}+, SSI+/ATB_{po}- and SSI-/ATB_{po}-.
18 Descriptive statistics included n (%) and median [interquartile range] for categorical and
19 continuous variables, respectively. Categorical variables were compared across groups using
20 Pearson's chi-square test or Fisher's exact test, as appropriate. Continuous variables were
21 compared across groups using a Kruskal-Wallis test.

22 Multivariable logistic regression was performed to pick up factors associated with SSI
23 occurrence. As regards the low number of events and in order to avoid over-adjustment, we
24 only included in the multivariable model factors significantly associated with SSI occurrence

1 in univariate analysis, and severity score. The goodness-of-fit of the model was checked using
2 the McFadden's R^2 test [18].

3 A 0.05 p-value threshold was considered significant. The analysis was conducted in R [19]
4 and figures were produced using the package ggplot2 [20].

5

6 **Results**

7 *Patient characteristics according to surgery*

8 From 2007 to 2018, 165 patients underwent scheduled major pancreatic surgery. Sixteen
9 patients were excluded because of the absence of medical files, and data from 149 patients
10 (115 PD and 34 DPS, 57.7% men) were finally analyzed. The median age was 68 [60-77]
11 years. The median SOFA score at admission was 2 [2-5] and the median SAPS II was 23 [18-
12 30]. PD and DPS patients had similar characteristics. Forty-two PD patients (36.8%) had a
13 bile duct prosthesis, whereas none of the DPS patients had such a medical device.
14 Neoadjuvant chemotherapy was less frequently noted in PD than in DPS patients (10.4%
15 versus 30.3%, respectively; $p=0.01$). ATB_{po} was more frequently prescribed in PD than in
16 DPS patients (33.9% versus 8.8%, respectively; $p=0.006$). In-hospital mortality was 3.5% and
17 similar in both groups. The global occurrence of postoperative infectious complications (SSI,
18 bacteremia, pneumonia) was 26.8% and did not differ between PD and DPS patients (27%
19 versus 26.5%, respectively; $p=1$).

20 *SSI and postoperative prescription of antibiotics*

21 Thirty patients (20.1%) experienced SSI after a median time interval of 10 [5, 12] days. The
22 comparison between patients with and without SSI is shown in **table 1**. The incidence of SSI
23 was constant over time (**Figure**). Forty-two patients (28.2%) received ATB_{po} . We found no
24 difference in ATB_{po} between patients with and without SSI (26.7% versus 28.6%,
25 respectively; $p=0.9$). Postoperative fever was significantly associated with SSI ($p<0.001$),

1 while the prevalence of preoperative biliary prosthesis was similar in patients SSI+ and SSI-
2 (37.9% versus 26.7%, respectively; $p=0.34$). The comparison between patients with and
3 without ATB_{po} is presented in **table 2**.

4 One hundred and seven patients (71.8%) did not receive ATB_{po}: 85/107 (79.4%) did not
5 develop an SSI while 22/107 (20.6%) did. In-hospital mortality was higher in these ATB_{po}-
6 /SSI+ compared to the ATB_{po}-/SSI- patients (18.2% versus 0.0%, respectively; $p=0.002$). A
7 biliary prosthesis was equally frequent in both groups (15.4% versus 28.6%, respectively;
8 $p=0.2$), while fever was more frequently noted in ATB_{po}-/SSI+ compared to the ATB_{po}-/SSI-
9 patients (72.7% versus 33.3%, respectively; $p=0.001$). A biliary prosthesis was more
10 frequently observed in ATB_{po}+/SSI- than in ATB_{po}-/SSI- patients (15.5% versus 52.9%
11 respectively; $p<0.0001$). Fever occurrence was similar in both ATB_{po}+/SSI- and ATB_{po}-/SSI-
12 patients (42.9% versus 41.5%, respectively; $p=1$).

13 In multivariable analysis, fever was the single independent factor associated with SSI
14 occurrence (odds ratio 6.24 [95% confidence interval 2.4, 18.6]) (**table 3**).

15 *Microbiological data*

16 Per-operative biliary drainage samples were collected and analyzed in 42 (28.2%) patients,
17 among which 30 (71.4%) were positive. The proportion of positive culture of the per-
18 operative biliary drainage sample did not differ between SSI+ and SSI- patients (Table 1).

19

20 **Discussion**

21 This study confirms that major pancreatic surgery is associated with a high rate of major SSI,
22 one in five patients experiencing this postoperative complication. In this cohort, ATB_{po} was
23 spared for more than half of the patients without impact on their outcome. Moreover, a similar
24 rate of ATB_{po} prescription was observed in patients with or without SSI, even if SSI could

1 have been prevented in ATB_{po} patients. Among the patients who had not received ATB_{po},
2 those who developed an SSI had a poorer outcome, but were notably more frequently febrile.
3 As previously described, our work confirms that the mortality rate is low in this kind of major
4 abdominal surgery [1, 3, 4], even if it is associated with high infectious morbidity. We found
5 levels of infectious events comparable to those previously published [2, 3, 4]. Nonetheless,
6 our results differ slightly from those of former studies concerning the risk factors associated
7 with the occurrence of SSI. First, ampulloma was not associated with an increased risk for
8 SSI. Moreover, we did not observe any association between bile duct prosthesis and SSI,
9 while such a device has been associated with postoperative infectious complications in
10 previous reports [6, 7, 21]. Bile duct instrumentation has already been associated with
11 microbial colonization of bile [6]. This is the why some authors recommend introducing
12 ATB_{po} after PD, with compelling results [3, 4]. Interestingly, our results suggest that the
13 presence of a biliary prosthesis was a trigger for the prescription of ATB_{po}, while we showed
14 no impact of such devices on the occurrence of SSI. Routine antibiotic prescription runs the
15 risk of the emergence of MDRO [22, 23] and of antibiotic-related morbidity, such as more
16 and more frequent anaphylaxis [24].

17 Our study was conducted in the new era of antibiotic stewardship designed to avoid
18 unnecessary exposure of patients to antibiotics, in order to prevent the emergence of resistant
19 bacteria [25], without negatively impacting outcomes. We demonstrated that 57% of the
20 patients were not exposed to antibiotics and had no SSI, while 14.8% might have been
21 protected from SSI by systematic prescription of antibiotics postoperatively. The poorer
22 outcome of the latter could be explained, at least in part, by a delay in antibiotic prescription,
23 which is known to be associated with mortality in the case of serious infections [26, 27]. In
24 contrast to routine antibiotic use, our work suggests that it may be possible to decrease the use
25 of antibiotics after scheduled major pancreatic surgery for a large proportion of patients,

1 provided there is no delay in antibiotic prescription in the case of postoperative fever. This
2 strategy is in accordance with those designed to combat the development and spread of
3 antimicrobial resistance, such as antimicrobial stewardship and infection prevention and
4 control [28].

5 We acknowledge several limitations. First, due to the retrospective design of the study, we
6 were unable to include 16 patients because their medical files were unavailable. However, the
7 proportion of missing data was very low in the analyzed observations, which gives us
8 confidence in the reliability of our results. Second, our cohort mixed PD and DPS.
9 Nevertheless, we found no significant difference between PD and DPS patients, suggesting
10 that major pancreatic surgery can be considered together. Moreover, it could be argued that a
11 preoperative endoscopic procedure is rarely needed in the case of DPS, which would justify
12 the exclusion of such patients, but our results showed no impact of the presence of a bile duct
13 prosthesis on the occurrence of SSI. Third, in this retrospective study postoperative antibiotics
14 were prescribed at the discretion of the physician in charge, which exposes us to the risk of
15 confounding by indication. Whatever the indication, it is difficult to interpret the ATB_{po}
16 patients since the SSI- patients were possibly protected while the SSI+ were assuredly treated
17 ineffectively. Our objective was to evaluate the possibility of sparing antibiotics and this is
18 why we decided to focus our results on the ATB_{po}- subgroup. The use of antibiotics after
19 pancreatic surgery is not challenged, but their timing and target population remain to be
20 defined. This study was not designed to address this major issue. In the same way, we did not
21 study the impact of the absence of antibiotic prescription on microbiota. These important data,
22 that could have strengthened our message, need to be evaluated further in this context. Lastly,
23 over the twelve-year duration of the study changes in usual practices such as surgical
24 procedure or indications for ATB_{po} may have occurred. This duration was chosen for two
25 important reasons. The first was that it corresponds to the timeframe when patients

1 undergoing a major pancreatic surgery were systematically hospitalized in the intensive care
2 unit. The second reason was to reach a sufficient number of patients to get relevant results,
3 even if the relatively small sample size could still be acknowledged as a limitation.

4

5 **Conclusion**

6 In the era of antimicrobial stewardship, our study shows that it is possible to avoid routine
7 prescription of antibiotics after scheduled major pancreatic surgery in more than one in two
8 patients, without impact on the occurrence of major SSI. Our results also demonstrate that
9 such a strategy exposes clinicians to the risk of deleterious under-prescription, which could be
10 salvaged by means of a strong clinical sign, such as postoperative fever. These results should
11 be validated in larger cohorts.

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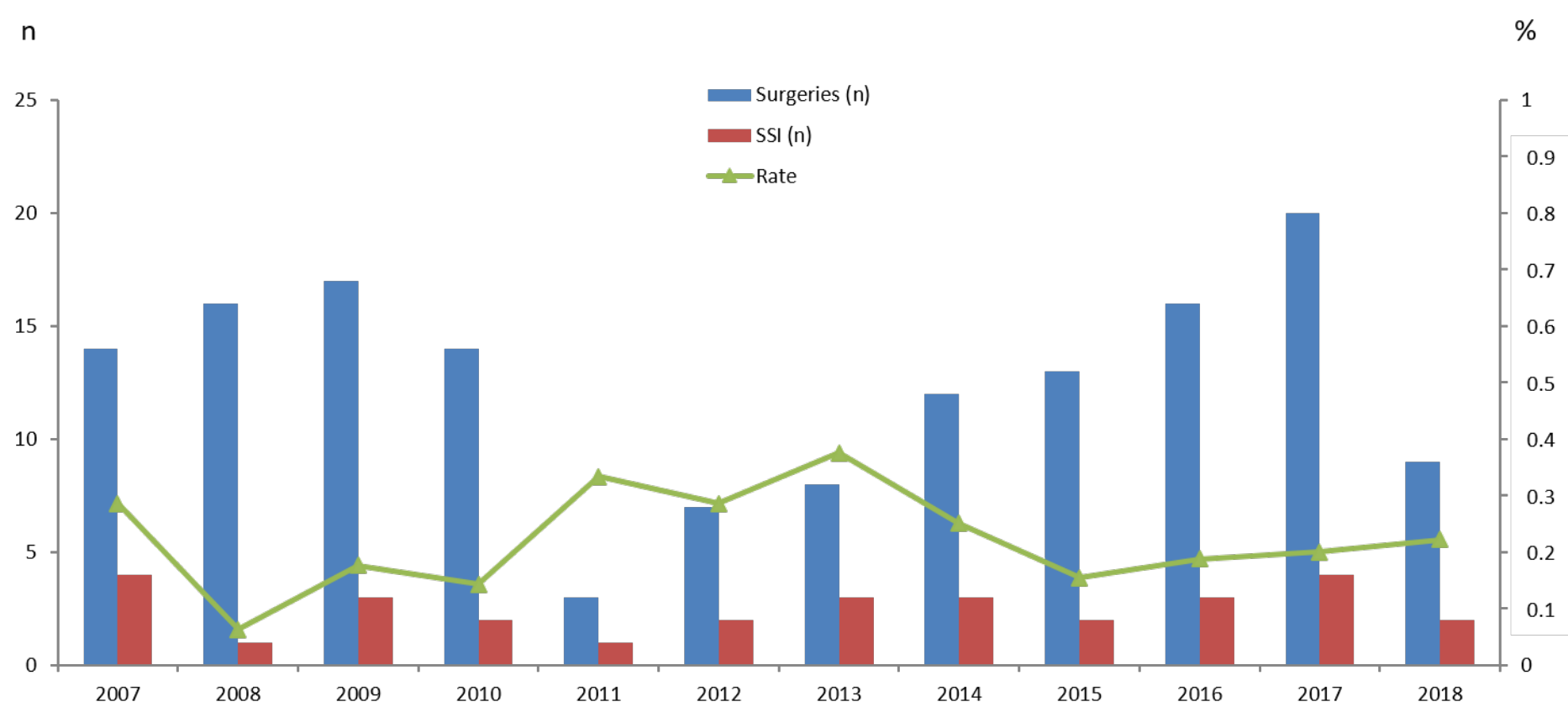
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19

1 **Legends of the figures:**

2 **Figure: Number of pancreatic surgeries and surgical site infections over time.**

3 Histograms represent the number of surgeries (blue bars) and surgical site infections (red
4 bars) during the period of the study (2007-2018). The green line represents the percentage of
5 surgical site infections over the time.

6



Surgical Site Infection	No (n=119)	Yes (n = 30)	p value
Age – years	69 [60;78]	64 [58;77]	0.49
Weight – kg	66 [56;78.5]	78 [67;90]	0.001
Simplified Acute Physiology Score II	23 [17.5;30]	27 [19;34]	0.28
Sequential Organ Failure Assessment	2 [1;4]	3 [2;5]	0.53
Chronic cardiac failure	3 (2.5)	0 (0)	1.00
Chronic arterial disease	2 (1.7)	2 (6.7)	0.18
Diabetes mellitus	25 (21)	6 (20)	1.00
Chronic obstructive pulmonary disease	7 (5.9)	1 (3.3)	1.00
Chronic kidney disease	6 (5)	3 (10)	0.39
Neoadjuvant chemotherapy	19 (16)	3 (10.3)	0.57
Bile duct prosthesis	31 (26.3)	11 (37.9)	0.31
Number of biliary prostheses			0.51
	0	87 (73.1)	19 (65.5)
	1	26 (21.8)	7 (24.1)
	2	6 (5)	3 (10.3)
Antibiotics within the preceding 3 months	15 (12.7)	7 (23.3)	0.16
Preoperative bacteremia	4 (3.4)	2 (7.1)	0.32
Preoperative bilirubin level - $\mu\text{mol.L}^{-1}$	20.5 [10;143]	20 [11;141.5]	0.79
Ampulloma	14 (15.9)	4 (19)	0.75
Positive culture of per-operative biliary drainage sample	22 (18.5)	9 (30)	0.2
Postoperative organ replacement therapy			
Mechanical ventilation	21 (17.6)	16 (53.3)	<0,001
Vasopressors	14 (11.9)	9 (30)	0,02
Renal replacement therapy	0 (0)	4 (13.8)	0,001
Systematic postoperative antibiotics	34 (28.6)	8 (26.7)	1.00
Fever	40 (33.9)	22 (73.3)	<0.001
Bacteraemia	10 (8.4)	11 (36.7)	<0.001

Pneumonia	16 (13.4)	6 (20)	0.5
Hospital mortality	1 (0.9)	4 (13.3)	0.007
Acquisition of multidrug resistant organisms	2 (2.1)	1 (3.7)	0.53

Table 1: Comparison between patients with and without surgical site infection.

Continuous variables are expressed as median [IQR] and categorical variables are expressed as n (%).

Systematic postoperative antibiotics	No (n=107)	Yes (n=42)	p value
Age – years	68.0 [60.5-76.0]	68.5 [58.0-79.0]	0.9
Weight – kg	69.5 [58.0;82.0]	69.0 [60.0;78.0]	0.914
Simplified Acute Physiology Score II	23.0 [18.0;30.0]	25.0 [18.0;31.0]	0.647
Sequential Organ Failure Assessment	2.0 [1.0; 4.0]	3.0 [2.0; 5.0]	0.067
Chronic cardiac failure	2 (1.9%)	1 (2.4%)	1
Chronic arterial disease	2 (1.9%)	2 (4.8%)	0.316
Diabetes mellitus	24 (22.4%)	7 (16.7%)	0.579
Chronic obstructive pulmonary disease	6 (5.6%)	2 (4.8%)	1
Chronic kidney disease	5 (4.7%)	4 (9.5%)	0.270
Neoadjuvant chemotherapy	19 (17.9%)	3 (7.1%)	0.160
Bile duct prosthesis	19 (18.1%)	23 (54.8%)	<0.001
Number of biliary prostheses			<0.001
	0	86 (81.1%)	20 (47.6%)
	1	15 (14.2%)	18 (42.9%)
	2	5 (4.7%)	4 (9.5%)
Antibiotics within the preceding 3 months	12 (11.3%)	10 (23.8%)	0.095
Preoperative bacteremia	1 (1.0%)	5 (12.2%)	0.007
Preoperative bilirubin level - $\mu\text{mol.L}^{-1}$	20.0 [10.0;144.5]	35.0 [12.0;142.0]	0.418
Ampulloma	10 (12.3%)	8 (28.6%)	0.089
Postoperative organ replacement therapy			
Mechanical ventilation	25 (23.4%)	12 (28.6%)	0.652
Vasopressors	15 (14.2%)	8 (19.0%)	0.624
Renal replacement therapy	4 (3.8%)	0 (0%)	0.325
Surgical site infection	22 (20.6)	8 (19.0)	1
Fever	44 (41.5%)	18 (42.9%)	1
Bacteraemia	15 (14.0%)	6 (14.3%)	1
Pneumoniae	20 (18.7%)	2 (4.8%)	0.057

Hospital mortality	4 (4.0%)	1 (2.4%)	1
Acquisition of multidrug resistant organisms	1 (1.1%)	2 (5.9%)	0.185

Table 2: Comparison between patients with and without systematic postoperative antibiotics.

Continuous variables are expressed as median [IQR] and categorical variables are expressed as n (%).

Table 3: Multivariate analysis of factors independently associated with surgical site infection.

Factor	Odds Ratio	P value
Simplified Acute Physiology Score II	1.00 [0.97-1.04]	0.9
Bile duct prosthesis	1.21 [0.44-3.18]	0.7
Fever	6.24 [2.4-18.57]	<0.001

Data are expressed as Odds Ratios [95% CI].