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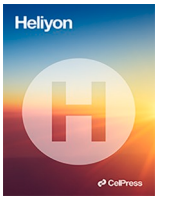

Prolonged cardiopulmonary bypass time as predictive factor for bloodstream infection

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ABSTRACT

Objectives: To evaluate the correlation between patient characteristics, operative variables and the risk of blood stream infection as well as the association of primary blood stream infection and adverse outcomes.
Methods: Clinical records of 6500 adult patients who underwent open heart surgery between February 2008 and October 2020 were analyzed. The microbiological pattern of the primary BSI and its association with adverse events, such as mortality and major cardiovascular events, were evaluated.
Results: Primary bloodstream infection was diagnosed in 1.7% (n = 108) of patients following cardiac surgery with the application of cardiopulmonary bypass. Most isolated bacteria were gram-negative bacillus groups, such as the Enterobacteriaceae family with Serrata marcescens in 26.26%, followed by the Enterococcaceae family with the *Enterococcus faecalis* in 7.39% and Enterococcus faecium in 9.14% as the most frequently identified bacteria. The postprocedural mortality, stroke rate $p < 0.001$, the incidence of postoperative new renal failure $p < 0.001$, and the renal replacement therapy $p < 0.001$ were significantly higher in the primary BSI group. Aortic cross-clamp time >120 min, OR 2.31 95%CI 1.34 to 3.98, perfusion time >120 min, OR 2.45 95%CI 1.63 to 3.67, and duration of the intervention >300min, OR 2.78 95%CI 1.47 to 5.28, were significantly related to the primary BSI.
Conclusion: The gram-negative bacillus was the most common microorganism identified in BSI after cardiovascular operations using cardiopulmonary bypass. Patients on dialysis prior to cardiac surgery are at higher risk for having BSI. Enteric bacterial translocation after prolonged cardiopulmonary bypass is a possible mechanism of early primary bloodstream infection in these patients. In patients at high risk, prophylactic use of an antibiotic regimen with broader gram-negative bacteria coverage should be considered, especially in those with prolonged cardiopulmonary bypass and intervention time.

1. Introduction

Infectious complications after cardiovascular surgery, especially in cardiopulmonary bypass (CPB) interventions, are associated with significant morbidity and increased perioperative mortality [1–5]. A perioperative mortality rate of up to 40% has been reported

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Nomenclature

Abbreviations

AUROC	area under the receiver operating characteristics
BSI	bloodstream infection
CBP	cardiopulmonary bypass
CI	confidence interval
CT	computer tomography
GNB	gram negative bacillus
LVEF	left ventricular ejection fraction
MACCE	major adverse cardiac and cerebrovascular events
MRI	magnetic resonance imaging
NYHA	new york heart association
OR	odds ratio
ROC	receiver operating characteristics
ST	the society of thoracic surgery
VARC	Valve Academic Research Consortium

in cases of bloodstream infection (BSI) in patients following cardiovascular surgeries [3].

The risk factors for postoperative infection after cardiovascular surgery using CPB have been identified, such as older age, diabetes mellitus, obesity, emergency surgery, multiple blood transfusions, postoperative low cardiac output, and the use of mechanical circulatory support devices [4–6]. Due to the increased risk of blood product transfusion and immunomodulatory effect, CPB use can be theoretically considered a risk factor for infection after a cardiovascular operation. Practice guidelines for the choice of prophylactic antibiotics and other preventive measures in patients undergoing cardiovascular operations have been established and are widely accepted [7,8]. Nevertheless, the microbiological pattern in patients with nosocomial infection, which continues to change in the current modern antibiotic era, has been rarely investigated [9,10]. Understanding the prevalence and associated risk factors for different causative microorganisms in patients undergoing cardiac surgery conducted with CPB should be emphasized.

We hypothesized that prolonged CPB usage predicts early bloodstream infection following cardiac surgery. This single-center retrospective study aimed to analyze demographics and microbiological factors of patients undergoing cardio surgical interventions with BSI.

2. Materials and methods

The local ethics committee at the University of Basel, Basel, Switzerland approved the study protocol (EKNZ 2020-00210, clinicaltrials.gov NCT04548167). Written informed consent was waived due to the retrospective nature of the study.

2.1. Patient populations

This retrospective study included all adult patients who underwent open heart surgery using CPB from February 2008 to October 2020. Patients with positive blood culture and evidence of newly developed septicemia during the index hospital stay were included. Exclusion criteria were as follows; active endocarditis, patients with indications such as left ventricle aneurysma, cardiac trauma, isolated congenital defect and left ventricular assist device (LVAD) implantation.

Patient records were selected from our institutional database (Dendrite), which is harmonized with the surgical planning tool and checked for completeness and consistency monthly.

2.2. Study outcome: definition of bloodstream infection

Primary BSI was defined as any finding of a microorganism from a blood sample without any evidence of any other infection site or potential infection entry region diagnosed within 30 days after surgery. This definition does not comprise common skin colonized microorganisms, such as coagulase-negative Staphylococci, Viridans group Streptococci, Corynebacterium species, Bacillus species, Propionibacterium species, and Aerococcus species or Micrococcus species, which were isolated from only a single blood sample, where contamination was suspected. Primary outcome of this study was BSI within 30 days. As a sensitivity analysis, we repeated the analysis for any finding of the same microorganisms within 7 days after surgery to maintain phenotypical primary BSI and avoid confounding, further referred to as early BSI.

All blood samples were taken from central and peripheral lines and/or phlebotomy. Blood cultures were drawn in case of suspected sepsis based on clinical and/or diagnostical evidence.

2.3. Perioperative prophylactic disinfection and antibiotic protocol

At our institution, all elective patients showered with octenidine-based skin cleanser (Octenisan®) wash lotion less than 24 h before the intervention. Preoperatively all patients are screened for MRSA. Afterward, the patient was transferred to the operating room, where a medical doctor was responsible for the disinfection. The first perioperative prophylactic antibiotic dosage was given before the surgical incision. According to the Society of Thoracic Surgery (STS) Practice Guidelines [7,8], all patients received six shots of 2nd generation cephalosporin within 48 h. In case of a previous allergic reaction to lactam or penicillin, vancomycin was used, usually with another antibiotic agent with additional gram-negative coverage. Prophylactic antibiotics were taken for 48 h postoperatively.

Postulating that the most common cause of surgical site infection is likely related to the colonized Staphylococcus, Vancomycin and third-generation cephalosporin were used as prolonged antibiotic therapy in patients with elevated risk for surgical site infection. Likely until the risk was eliminated, for example, in patients with open sternal wound until the wound has been closed.

2.4. Clinical parameters

In-hospital mortality was defined as death before discharge. A neurologic event was defined according to the Valve Academic Research Consortium-2 (VARC) [9] and a perioperative stroke was defined as a duration of a focal or global neurological deficit >24h or <24 h if available neuroimaging documents a new hemorrhage or infarct.

Aim of the study was analyze the demographics and microbiological factors of patients undergoing cardiac surgery using CPB complicated with primary BSI postoperatively. Secondary outcomes were the incidence of postoperative stroke, myocardial infarction during the hospitalization, and the incidence of composite adverse cardiac and cerebrovascular events (MACCE). MACCE was a composite endpoint of in-hospital mortality, stroke and myocardial infarction. The composite endpoints were defined according to the VARC [9].

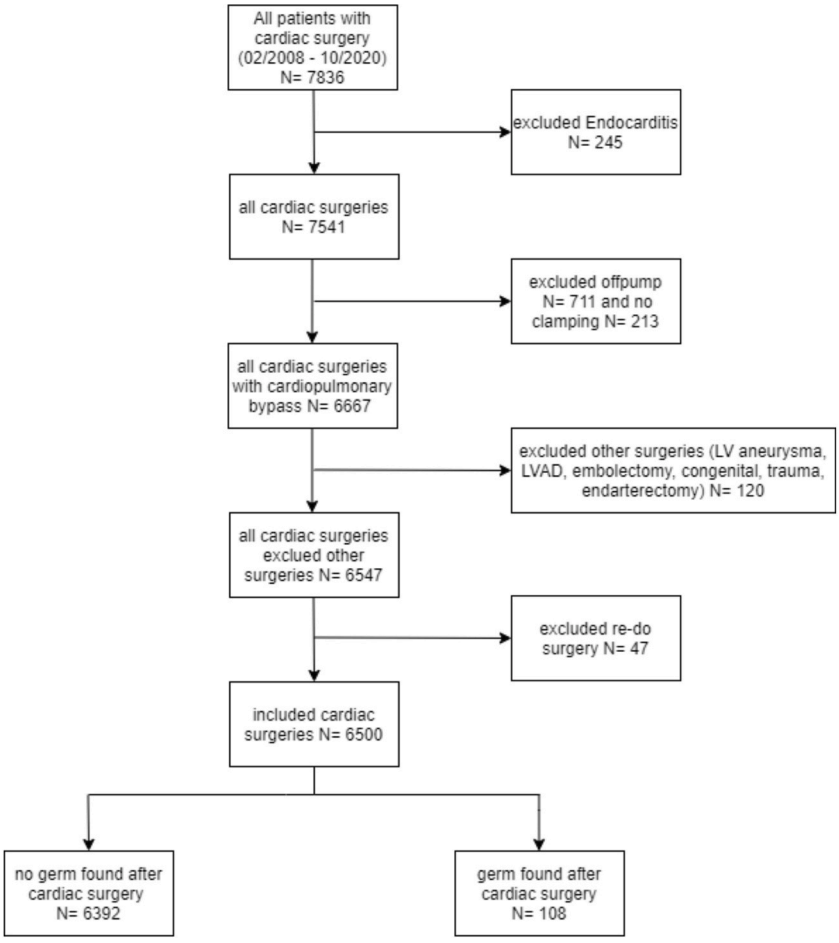

Fig. 1. Selection flow chart of patients undergoing cardiovascular operations using cardiopulmonary bypass
LVAD: left ventricular assist device.

2.5. Statistical methods

To investigate a crude association of our pre-specified prognostic variables, duration of operation, perfusion, or aortic clamping, with the risk of positive blood culture within 30 days after surgery, we first calculated odds ratios (OR) with 95% confidence intervals (CI) for categories of one or 2 h, respectively, according to the range and distribution of the predictive variable. We carried out nonparametric tests for trends among these ORs. We then calculated odds ratios per continuous increase of predictive variables using logistic regression, first crude then with adjustment. To avoid zero digits, ORs are expressed per 10-min increase. We back-transformed the crude odds to probabilities and plotted them against kernel density estimates of the distribution of the prognostic variable. For the adjustment, we included EuroSCORE, patient age, left ventricular ejection fraction (LVEF), as continuous covariates and type of cardiac surgery, diabetes, preoperative renal failure, New York Heart Association (NYHA) class III or IV, and emergency as categorical covariates. We plotted receiver operating characteristics (ROC) curves and calculated the area under the ROC curves (AUROC) to assess the predictive performance of duration, perfusion time, and clamping time. We repeated the main analysis for early BSI, e.g. BSI within 7 days after surgery.

Continuous variables were shown as mean ± sd or median with interquartile range, as appropriate, and were compared using Student's *t*-Test or Wilcoxon-Mann-Whitney test. Categorical variables were shown in percentages and tested using Fisher's exact test. For descriptive statistics, we grouped the cohort by the outcome. We refrained from applying weighting or matching methods by treatment (duration of cardio-pulmonary bypass time), as grouping would need a cut-off for which there is no evidence. Furthermore, the assumption that each patient would have a probability >0 to be in either group is not plausible. All analyses were carried out using Stata 16 (Stata Corp., College Station, Texas).

3. Results

Between February 2008 and October 2020, 7836 adult patients older than 18 underwent cardiac surgery. In the analysis, we included 6500 patients. Positive bloodstream infection was confirmed in 355 (5.46%) patients, whereas according to the exclusion criteria, 247 cases were not included in the final analysis. Primary BSI was found in 108 (1.7%) patients within the first 30 days. The patient enrolment flowchart is presented in Fig. 1. The demographics of patients included in the analysis are presented in Table 1.

Overall, patients with primary BSI were older ($p < 0.001$), had more frequently diabetes mellitus ($p < 0.001$), had a history of myocardial infarction ($p = 0.002$) and were on dialysis ($p < 0.001$). Patients with BSI were more often diagnosed with renal impairment $p < 0.001$ pre-intervention and were more frequently diagnosed with heart failure (NYHA > III) $p < 0.001$. Patients with primary BSI had significantly lower left ventricular ejection fraction $p < 0.001$ (Table 1).

The microbiological findings of cases with primary BSI are presented in Table 2. In 86.1% of cases, a single bacteria was identified, whereas two different bacteria were identified in 12.9% and three bacteria in 0.9% of the cases. The Serrata marcescens was the most frequently identified bacteria in 32.4% of the cases, followed by *Enterococcus faecalis* in 12% and Klebsiella pneumonia, Enterococcus faecium, *Escherichia coli*, and *Enterobacter cloacae* all in 8.3% of the cases. The Enterobacteriaceae family was the most frequently identified bacteria family, found in 66.5% of the cases, followed by Enterococcacea in 16.5% and Morganellaceae and

Table 1
Patient characteristics.

	Total (N = 6500)	No BSI (N = 6392)	BSI (N = 108)	p
Age	66 ± 11	66 ± 11	70 ± 10	<0.001
Female	1592 (24%)	1568 (25%)	24 (22%)	0.65
Diabetes	1691 (26%)	1645 (26%)	46 (43%)	<0.001
CAD	3080 (47%)	3029 (47%)	51 (47%)	1.00
Main stem disease	951 (15%)	934 (15%)	17 (16%)	0.68
Peripheral artery disease	588 (9.0%)	572 (8.9%)	16 (15%)	0.042
Preoperative Stroke	534 (8.2%)	522 (8.2%)	12 (11%)	0.29
Preoperative renal impairment	386 (5.9%)	366 (5.7%)	20 (19%)	<0.001
Terminal renal impairment with dialysis	73 (1.1%)	66 (1.0%)	7 (6.5%)	<0.001
COPD	765 (12%)	747 (12%)	18 (17%)	0.13
History of MI	2164 (33%)	2107 (33%)	57 (53%)	<0.001
Hypertension	5093 (78%)	4997 (78%)	96 (89%)	0.006
Hypercholesteremia	3935 (61%)	3864 (60%)	71 (66%)	0.28
NYHA				<0.001
n/a	887 (14%)	875 (14%)	12 (11%)	
I	1270 (20%)	1255 (20%)	15 (14%)	
II	2283 (35%)	2253 (35%)	30 (28%)	
III	1753 (27%)	1718 (27%)	35 (32%)	
IV	307 (4.7%)	291 (4.6%)	16 (15%)	
NYHA ≥ III	2060 (32%)	2009 (31%)	51 (47%)	<0.001
AF preop.	615 (9.5%)	601 (9.4%)	14 (13%)	0.24
Current Smoker	1324 (20%)	1300 (20%)	24 (22%)	0.63
LVEF	54 ± 12	54 ± 11	48 ± 15	<0.001

BSI: blood stream infection, CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; MI: myocardial infarction; NYHA: New York heart association; AF: atrial fibrillation; LVEF: left ventricular ejection fraction.

Table 2
Relevant bacteria identified in primary blood stream infection.

	Any finding	Single finding	Double finding	Triple finding
	N = 108	N = 93	N = 14	N = 1
Serratia marcescens	35	32	3	0
Enterococcus faecalis	12	7	4	1
Enterobacter cloacae group	9	5	3	1
Enterococcus faecium	9	6	3	0
Escherichia coli	9	6	3	0
Klebsiella pneumoniae	9	8	1	0
Pseudomonas aeruginosa	8	6	2	0
Klebsiella oxytoca	7	4	3	0
Enterobacter aerogenes	4	3	1	0
Citrobacter koseri	3	2	0	1
Eggerthella lenta	3	1	2	0
Morganella morganii	3	2	1	0
Actinomyces species	2	2	0	0
Klebsiella aerogenes	2	2	0	0
Acinetobacter ursingii	1	1	0	0
Bacteroides thetaiotaomicron	1	1	0	0
Clostridium innocuum	1	0	1	0
Gemella species	1	1	0	0
Granulicatella adiacens	1	1	0	0
Prevotella melaninogenica/oralis	1	1	0	0
Proteus mirabilis	1	1	0	0
Proteus vulgaris	1	0	1	0
Ruminococcus gnavus	1	1	0	0

Number of bacteria found per patient.

Pseudomonadaceae family in 6.22%. The microbiological finding was positive on gram-negative bacillus (GNB) in 79.6% of cases.

Surgical details are presented in Table 3. In the BSI group, the combined interventions were performed more often ($p < 0.001$) compared to the no BSI group, and there were more emergency procedures ($p < 0.001$). The intervention duration ($p < 0.001$), the aortic cross-clamp time ($p < 0.001$), and cardiopulmonary bypass time ($p < 0.001$) were significantly longer compared to the group with no evidence of infection (Table 3).

Hospital outcomes are summarized in Table 4. The in-hospital mortality and the incidence of perioperative myocardial infarction and stroke were significantly higher in the primary BSI group ($p < 0.001$). The intensive care unit stay and the incidence of prolonged intubation ($p < 0.001$) were longer in the BSI group. The incidence of MACCE was significantly higher in the primary BSI ($p < 0.001$) group.

Prolonged cross-clamp time, prolonged perfusion time and prolonged intervention time were significantly associated with an elevated risk of primary BSI (Table 5). The perfusion time >120 min, OR 2.45 (1.63 to 3.67); aortic cross-clamp time >120min, OR 2.31 (1.34 to 3.98); and intervention time >300min, OR 2.78 (1.47 to 5.28), were related to primary BSI (Table 5).

The receiver operating characteristic curve for cross-clamp time, perfusion time, and consequently the intervention time showed areas under curves of 0.58 (95%CI 0.53 to 0.64), 0.66 (95%CI 0.60 to 0.71), and 0.64 (95%CI 0.59 to 0.70) for primary BSI (Fig. 2).

Concerning all main prognostic variables, ORs for primary BSI increased monotonically compared to the lowest category, which we used as a reference, exhibiting a nonparametric trend, see also Table 5. For the duration of operation (Fig. 3A), perfusion time (Fig. 3B) and aortic clamping time (Fig. 3C), the increase became significant only for higher categories, indicating that risk increased in a relatively small subgroup at the upper tail of the distribution (Fig. 3).

Table 3
Operative variables.

	Total (N = 6500)	No BSI (N = 6392)	BSI (N = 108)	p
Type of surgery				0.002
CABG	2693 (41%)	2658 (42%)	35 (32%)	
CABG&Valve(s)	1114 (17%)	1083 (17%)	31 (29%)	
Valve(s)	1583 (24%)	1565 (24%)	18 (17%)	
Aortic surgery	1110 (17%)	1086 (17%)	24 (22%)	
Emergency	681 (10%)	652 (10%)	29 (27%)	<0.001
Additive EUROScore	6.4 ± 3.7	6.4 ± 3.7	10 ± 4.1	<0.001
Logistic EUROScore	10 ± 14	10 ± 13	23 ± 21	<0.001
Euroscore II	2.1 [1.1 to 4.8]	2.1 [1.1 to 4.6]	6.3 [3.2 to 19]	<0.001
Intervention Time (min)	218 ± 66	217 ± 65	260 ± 90	<0.001
Cardiopulmonary bypass time (min)	118 ± 48	117 ± 47	151 ± 69	<0.001
Aortic cross clamping time (min)	79 ± 35	79 ± 34	91 ± 41	<0.001

BSI: blood stream infection, CABG: coronary artery bypass graft.

Table 4
In hospital outcomes.

	Total (N = 6500)	No BSI (N = 6392)	BSI (N = 108)	p
Operative mortality	235 (3.6%)	203 (3.2%)	32 (30%)	<0.001
Length of ICU stay, days	2.0 [1.0 to 3.0]	2.0 [1.0 to 3.0]	13 [5.0 to 23]	<0.001
Intubation >72h	281 (4.3%)	235 (3.7%)	46 (43%)	<0.001
Reoperation for bleeding	272 (4.2%)	259 (4.1%)	13 (12%)	<0.001
Postoperative MI	122 (1.9%)	115 (1.8%)	7 (6.5%)	0.004
Postoperative Stroke	259 (4.0%)	243 (3.8%)	16 (15%)	<0.001
AF at discharge	1885 (29%)	1833 (29%)	52 (48%)	<0.001
Permanent pacemaker	274 (4.2%)	264 (4.1%)	10 (9.3%)	0.024
Sternal infection	122 (1.9%)	109 (1.7%)	13 (12%)	<0.001
Postoperative renal failure	553 (8.5%)	503 (7.9%)	50 (46%)	<0.001
Renal replacement therapy	173 (2.7%)	148 (2.3%)	25 (23%)	<0.001
Pulmonary infection	465 (7.2%)	415 (6.5%)	50 (46%)	<0.001
MACCE	545 (8.4%)	499 (7.8%)	46 (43%)	<0.001
Sepsis	155 (2.4%)	105 (1.6%)	50 (46%)	<0.001
Length of stay	9.0 [7.0 to 12]	8.0 [7.0 to 12]	22 [14 to 36]	<0.001

BSI: blood stream infection, ICU: intensive care unit; MI: myocardial infarction; AF: atrial fibrillation; MACCE: major adverse cardiac and cerebrovascular events.

Table 5
Time categories and outcome.

Category	N	events	OR	P	P*
Intervention time (min)					
≤180	2232	24	Reference		<0.001
>180 to 300	3657	61	1.56 (0.97 to 2.51)	0.066	
>300 to 420	545	16	2.78 (1.47 to 5.28)	0.002	
>420	66	7	10.9 (4.52 to 26.3)	<0.001	
Perfusion time, (min)					
≤120	3944	40	Reference		<0.001
>120 to 240	2411	59	2.45 (1.63 to 3.67)	<0.001	
>240	145	9	6.46 (3.07 to 13.6)	<0.001	
Aortic clamping time, (min)					
≤60	2170	30	Reference		0.008
>60 to 120	3566	54	1.10 (0.70 to 1.72)	0.687	
>120	764	24	2.31 (1.34 to 3.98)	0.002	

OR: odds ratio. P* relates to non-parametric trends.

Table 6 shows crude and multivariable odds ratios (ORs) for our main prognostic variables and outcome. Duration of operation was associated with a small increase in the risk of the outcome. More specifically, risk of BSI increased by 0.12% per 10 min increase in the duration of the operation corresponding to an OR of 1.07, given the overall risk of BSI being 1.7% (e.g. 108/6500). Adjusting for EuroSCORE and variables in the full model reduced this increase to 0.084%, yielding robust results. We found the same pattern for perfusion and clamping time.

Sensitivity analysis of risk elements for early BSI, e.g. primary BSI during the first 7 days following intervention is presented in supplementary materials. We found early BSI in 49 (0.75%) patients. The relative frequency of bacteria was similar to our main analysis, and all associations showed a similar pattern, however with smaller statistical power due to small number of patients in the early BSI group.

4. Discussion

In this retrospective data analysis, the gram-negative bacillus (GNB) was the predominant cause of primary BSI in patients undergoing open heart surgery using CPB. More than 60% of the identified bacteria belonged to the Enterobacteriaceae family, followed by the Enterococcaceae family in 16.5% of the cases, the two most representative gut flora bacteria. The primary BSI was strongly related to the prolonged cross-clamp and cardiopulmonary bypass time.

The incidence of primary BSI following cardio surgical procedure associated with the GNB infection is considerable, ranging from 18% to 70% [10–15]. Unfortunately, in most reports, primary and secondary BSI are not differentiated, and hence does not reflect the different pathological pathways. According to the recent healthcare-associated infections (HAI), septicemia associated with a well-defined site of infection is classified as secondary BSI, whereas primary BSI is defined as an event with positive microbiological findings without evidence of another site of infection [15]. Consequently, the incidence of primary BSI following cardiac surgery may be wrongly assessed.

Ryna et al. set the primary BSI as any infection <96 h post cardiac surgery. Of 16 cases, 13 (81.3%) were GNB-related infections [10]. The time frame for the primary BIS was set to no more than 96 h post-intervention, an element that definitively restricted the

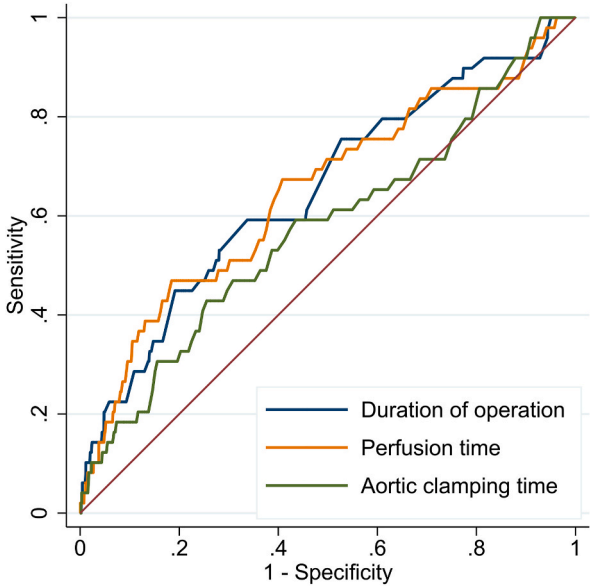

Fig. 2. Receiver operation characteristics curve of main prognostic variables such as duration of operation, cardiopulmonary bypass time and aortic clamping time. Area under the curve were as follows for duration of operation; 0.64 (0.59 to 0.70), for perfusion time; 0.66 (0.60 to 0.71) and for aortic clamping time; 0.58 (0.53 to 0.64).

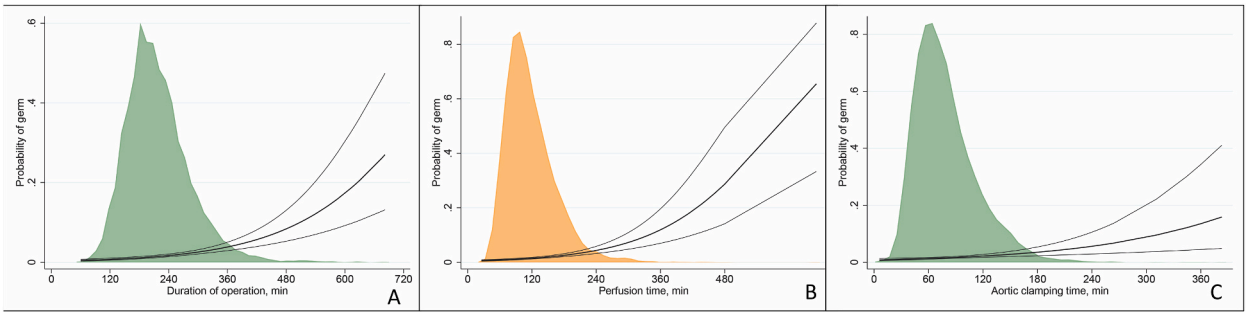

Fig. 3. Distribution of main prognostic variables and of outcome; 3A) Distribution of operation duration and outcome probability, 3B) Distribution of perfusion time and outcome probability, 3C) Distribution of Aortic clamping time and outcome probability.

results. Authors postulated that disrupting the mucosal-blood barrier in the gastrointestinal tract resulted in bacterial translocation, which would explain the high prevalence of GNB in primary BSI. Loss of intestinal barrier function is considered to play a key role in the onset of systemic inflammatory response syndrome, and it may be associated with intestinal ischemia-reperfusion injury [16]. Ischemia-reperfusion injury is caused by various pathological conditions that involve a critical reduction of blood flow to the intestine, such as acute obstruction of mesenteric arterial blood flow, hypoperfusion associated with major vascular or abdominal surgical procedures, and hemorrhagic shock or reduced intestinal perfusion during the CPB [17,18]. Indeed, splanchnic perfusion may be reduced during the CPB, and the prolonged CPB time may induce intestinal injury [19]. Moreover, the ischemic reperfusion injury following CPB may damage the intestinal mucosal barrier [20].

In our study, mainly intestinal flora, predominantly the Enterobacteriaceae family, caused the primary BSI following cardiac surgery with CPB, supporting the assumption of perioperative endogenous bacterial translocation as the predominant etiology after prolonged CPB.

The duration of intestinal hypoperfusion on CPB as catalysat or for ischemic injury as a key mechanism of bacterial translocation is an important factor to discuss. It was shown in an experimental setting that the extent of the ischemic mucosal injury is time-dependent. Specifically, a mesenteric hypoperfusion of 60 min results in loss of epithelium from the upper third of the intestinal villus, whereas ischemia of 120 min or more results in near-complete loss of epithelium and considerable damage to the lamina propria [21]. In our statistical model, where the perfusion time and cross-clamp time of more than 120 min were strongly associated with the increased risk for primary BSI, any prolongation of cross-clamp time and/or of the perfusion time on CPB considerably augmented the risk of primary BSI.

Restoring the intestinal barrier is a complex mechanism and is one of the key elements in regulating the uncontrolled translocation

Table 6
Crude and multivariable odds ratios (ORs) for our main prognostic variables and primary blood stream infection.

Outcome	Adjustment	OR (95% CI)	p
Operation duration, 10 min	Crude	1.07 (1.05 to 1.09)	<0.001
	adj. logisticeuroscore	1.05 (1.02 to 1.07)	<0.001
	adj. age	1.07 (1.05 to 1.09)	<0.001
	adj. diabetes	1.07 (1.05 to 1.09)	<0.001
	adj. preoprenalfailure	1.07 (1.05 to 1.09)	<0.001
	adj. NYHA III-IV	1.07 (1.05 to 1.09)	<0.001
	adj. LVEF	1.07 (1.05 to 1.09)	<0.001
	adj. emergency	1.06 (1.04 to 1.09)	<0.001
	adj. CABG	1.07 (1.04 to 1.09)	<0.001
	adj. full model[a]	1.05 (1.03 to 1.08)	<0.001
Perfusion time, 10 min	Crude	1.10 (1.07 to 1.12)	<0.001
	adj. logisticeuroscore	1.07 (1.04 to 1.10)	<0.001
	adj. age	1.10 (1.07 to 1.13)	<0.001
	adj. diabetes	1.10 (1.07 to 1.13)	<0.001
	adj. preoprenalfailure	1.09 (1.07 to 1.12)	<0.001
	adj. NYHA III-IV	1.09 (1.06 to 1.12)	<0.001
	adj. LVEEF	1.10 (1.07 to 1.13)	<0.001
	adj. emergency	1.09 (1.06 to 1.12)	<0.001
	adj. CABG	1.09 (1.06 to 1.12)	<0.001
	adj. full model	1.08 (1.05 to 1.12)	<0.001
Aortic clamping time, 10 min	Crude	1.08 (1.04 to 1.13)	<0.001
	adj. logisticeuroscore	1.05 (1.01 to 1.10)	0.029
	adj. age	1.09 (1.04 to 1.14)	<0.001
	adj. diabetes	1.09 (1.04 to 1.14)	<0.001
	adj. preoprenalfailure	1.08 (1.04 to 1.13)	<0.001
	adj. NYHA III-IV	1.08 (1.03 to 1.13)	0.001
	adj. LVEF	1.09 (1.04 to 1.14)	<0.001
	adj. emergency	1.08 (1.04 to 1.13)	<0.001
	adj. CABG	1.06 (1.01 to 1.12)	0.030
	adj. full model	1.07 (1.01 to 1.13)	0.014

NYHA: New York heart association; LVEF: left ventricular ejection fraction, CABG: coronary artery bypass graft.
Note that ORs are expressed per 10 min increase to avoid zero digits.
[a] Full model comprises all variables adjusted for one by one, hence all variables shown in the table.

of noxa. Repairing the intestinal surface integrity is a complex process that depends on several elements. We postulated that vasoconstrictive drugs might affect the restoration process besides the extant intestinal damage of individual vascular status resulting in unequally distributed flow in splanchnic vessels.

In our study, the time frame to investigate the primary BSI incidence was set to 30 days, and this arbitrarily defined period is debatable.

Recent literature has postulated that the intestinal barrier after CPB is restored a few days after intervention [22]. However, our sensitivity analysis revealed that the GNB with the predominant Enterobacteriaceae family was the main microbiological finding in patients with primary BSI up to 7 days post-intervention. Besides, primary BSI occurred in more than 50% of the included population after 7 days post-intervention, with the peak incidence between days 10 and 14. Intestinal barrier damage repair in patients with prolonged CPB is much more time-consuming, resulting in prolonged noxa translocation.

Consequently, efforts to prevent and adequately treat GNB-related BSI after cardiac surgery should be emphasized and might require adjustments. The first generation of cephalosporin is widely used as the first choice of prophylactic antibiotic therapy in patients undergoing cardiac surgery, and it was proven that the second generation of cephalosporine could reduce gram-positive and gram-negative infection after cardiac surgery [23].

In our study, more than half of the isolated Enterobacteriaceae were Enterobacter species. Based on the antibiotic sensitivity results from patients undergoing cardiac surgery and our institutional database, the Enterobacter species is generally resistant to first-generation and second-generation cephalosporins. Consequently, applying a third-generation or even fourth-generation cephalosporin as a prophylactic antibiotic regimen against both gram-negative and gram-positive bacteria in patients with prolonged CPB should be reasonable. That's why there is a need for further prospective randomized trials focusing on the strategy of antibiotic therapy in the field of cardiac surgery. In high-risk patients with infectious complications, even with the use of the third-generation or fourth-generation cephalosporin prophylaxis, a prompt escalation to a carbapenems-based antibiotic regimen could provide even better GNB coverage (i.e., covering GNBs with extended-spectrum b-lactamases) as an adaptive stepwise choice. However, the routine use of carbapenems to treat infectious complications after cardiac surgery before a definite culture result should be appraised with careful microbiological monitoring to prevent the emergence of multidrug-resistant GNB.

Some limitations should be considered when interpreting these findings. First, this is a single center retrospective study and there is a lack of random assignment. Second, we defined the timepoint of blood stream infection within 30 days after cardiac surgery. One should consider that potential confounders could mediate the connection between long bypass times and bacteremia, considering that the infection period was defined as 30 days post-op, The patients with long bypass times have longer lengths of stay and require more

support than patients without long bypass times. However the subgroup analysis of patients with BSI till 7th postoperative day, provided similar results.

Further to tackle the mentioned potential limitation and to validate our results a larger randomized controlled study should be conducted in future. Additionally one should as well keep in mind that the practice of routinely collecting specimens via indwelling catheters must be acknowledged to involve a risk of false positives and is problematic because of colonization of lines [24,25]).

5. Conclusion

Operative variables such as surgery over 5 h duration, aortic cross clamp of 120 min or cardiopulmonary time greater than 240 min as well as patient characteristics, especially preoperative need for hemodialysis were associated with increased risk of primary blood stream infection. Primary blood stream infection at out institution after cardiac surgery was most commonly caused by gram negative bacteria. Current guidelines for perioperative prophylaxis recommend first and second generation cephalosporins, which are not routinely effective against gram negative bacteria. Further prospective study is needed to determine the mechanism for BSI after cardiac surgery to improve the outcome for at risk patients.

Production notes

Author contribution statement

Constantin Mork MD.; Brigita Gahl PhD,; Friedrich Eckstein MD,; Denis A. Berdajs MD: Conceived and designed the experiments, performed the experiments, Analyzed and interpreted the data, Contributed reagents, materials analysis tools or data; Wrote the paper.

Data availability statement

Data will be made available on request.

Additional information

No additional information is available for this paper.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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