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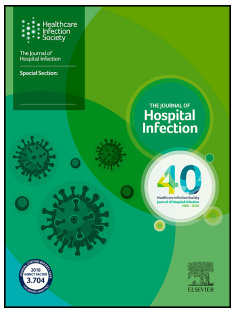

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Prevalence of enterococcal groin colonization in patients undergoing cardiac interventions: Challenging antimicrobial prophylaxis with cephalosporins in TAVR patients

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Running title: Enterococcal groin colonization in TAVR patients

Declarations of interest: None

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Structured summery

Background: Cephalosporins are recommended for prophylaxis before transcatheter aortic valve replacement (TAVR). Infective endocarditis (IE) after TAVR is caused by enterococci in up to 30%, especially early after TAVR. Enterococcal colonization in the groin has been postulated as a source of infection, not only because prophylaxis is not covering enterococci but also because most TAVR are performed by transfemoral access. There are few data analysing the groin microbiome to demonstrate the presence of enterococci.

Aim: To assess prevalence of enterococci in groins of cardiological patients receiving transfemoral interventions.

Methods: Prospective cohort study at the University Hospital Basel, Switzerland, between February and August 2020. From consecutive patients with transfemoral cardiac interventions two skin swabs from the groin were taken before antibiotic prophylaxis was administered: each one before/after groin disinfection. Swabs were analysed in the local microbiological laboratory following validated culture methods.

Findings: Of 290 included patients, 245 (84.5%) received coronary angiography, 31 (10.7%) TAVR, eight (2.8%) right heart catheterization, five (1.7%) closure of patent foramen ovale, one (0.3%) MitraClip®. In 48 patients, enterococci were detected before disinfection, in three, enterococci were still cultured after disinfection, and in one enterococci were only detected after disinfection. Enterococcal prevalence was 16.6% before and 1.4% after disinfection. Patients colonized with enterococci had a significantly higher body mass index and more often were diabetic.

Conclusion: Common enterococcal colonization of the groin coupled with frequently isolated enterococci from patients with TAVR-associated IE provide strong evidence to replace currently recommended antimicrobial prophylaxis with cephalosporins before TAVR with a compound that is active against enterococci.

Key words: Groin, colonization, cardiological, patients, enterococci, TAVR

Background and objectives

Transcatheter aortic valve replacement (TAVR) has become a standard procedure to treat patients with symptomatic, severe aortic stenosis. Initially, the indication for TAVR was restricted to elderly patients suffering from multiple comorbidities considered to be inoperable or at specific high-risk for surgical aortic valve replacement (SAVR); today, the literature supports the use of TAVR also in patients at intermediate- and low-risk for SAVR [1-3].

A well-known and potentially deadly complication after TAVR is infective endocarditis (IE), which occurs at an incidence rate of 1.0 per 100 person-years (95% confidence interval (CI) 0.85 to 1.17) similar to rates of prosthetic valve endocarditis (PVE) after SAVR [1, 2, 4, 5]. However, rates of mortality are high and considered much higher in IE after TAVR than in PVE [6, 7]. Additionally, the most common pathogens involved are quite different: early PVE within a year of SAVR, is likely the result of peri-procedural bacterial contamination and includes *Staphylococcus aureus*, coagulase-negative staphylococci, and rarely gram-negative bacteria or fungi, whereas late PVE after one year of SAVR is the result of haematogenous seeding, and organisms usually mimic those of native valve endocarditis with streptococci and staphylococci [8]. In contrast, enterococci are two to three times more frequent in IE after TAVR compared to SAVR; and in patients with early IE after TAVR (within 100 days) enterococci account for even one third of all IE events [6, 7, 9]. To prevent peri-operative infection or device contamination, the Centres for Disease Control and Prevention as well as the American Heart Association (AHA) recommend the routine administration of a single pre-operative dose of antimicrobial prophylaxis [8, 10, 11]. The antimicrobial compound should cover the most observed pathogens and bactericidal concentrations should be established at the time of incision. Current guidelines by AHA recommend antimicrobial prophylaxis before TAVR but downgraded the recommendation from B (moderate quality) to C (limited data) [8].

Abbreviations: AHA, American Heart Association; IE, infective endocarditis; ISCVID, International Society for Cardiovascular Infectious Diseases; PFO, patent foramen ovale; PVE, prosthetic valve endocarditis; RHC, right heart catheterization; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement

TAVR is commonly performed using a transfemoral access, explaining intuitively in part the predominance of enterococci. Additionally, patient characteristics such as advanced age and comorbidities may also predispose to enterococcal colonization by frequent healthcare contacts, and presumably higher antibiotic exposures, particularly cephalosporins. However, there is little or no data analysing the microbiome colonizing the groin area to demonstrate presence of enterococci: Byrd et al. did not even mention enterococci as part of the normal human skin microbiome [12]. A review on IE from AHA comparing SAVR and TAVR, reports enterococci as offending organisms in 24.6% in TAVR, *"which is different from surgery because of groin access"*, without any documentation or citation of this statement [8]. The current AHA guideline, as wells as an expert consensus document on TAVR recommend a cephalosporin before TAVR, possibly extrapolated from SAVR [8, 13]. In contrast, guidelines published in 2021 by our group recommend an adapted prophylaxis with activity against enterococci [14].

The aim of the present study was to assess prevalence of enterococci in cardiological patients receiving transfemoral coronarography or TAVR.

Patients and methods

This prospective cohort study was performed at the University Hospital Basel, Switzerland, between February and August 2020. The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). The study protocol was approved by the local ethics committee (EKNZ2020-02380) as part of a quality assurance project; therefore, individual informed consent was waived.

At predefined days, consecutive adult patients (≥ 18 years) receiving transfemoral TAVR, coronary angiography, MitraClip®, percutaneous closure of patent foramen ovale (PFO) or right heart catheterization (RHC) were included. During the study period, 1354 patients underwent

coronary angiography, 89 RHC, 100 received transfemoral TAVR, 10 were treated with MitraClip® and 28 had PFO closure. In patients with multiple interventions, only the first intervention during the hospital stay was considered for this study. Due to the SARS-CoV-2 pandemic, patient inclusion was interrupted several times on request of the hospital administration. Patients with non-transfemoral access, incomplete clinical data, missing groin swab culture results or earlier decline of the hospital general research consent for the use of routinely obtained personal and medical data were excluded.

In patients receiving an implant, single shot pre-interventional antimicrobial prophylaxis was administered with amoxicillin/clavulanic acid 2.2g for TAVR (changed from cephalosporin mid-2017 [14]) and cefuroxime 1.5g for MitraClip® or PFO closure. Prophylaxis was always administered after groin swabs were taken.

Baseline characteristics were collected by a standardized case report form and included demographics, comorbidities, immunosuppression (i.e. prednisone equivalent > 10 mg per day for ≥ 4 weeks, biologicals, immunosuppressive drugs (e.g., calcineurin-inhibitors, mTOR-inhibitors), chemotherapy within the preceding four weeks, presence of neutropenia (< 0.5 G/l), solid organ, or haematological stem cell transplantation), presence of urinary catheters or antibiotic treatment at the intervention time, EuroSCORE, and laboratory parameters.

Two skin swabs from the groin were taken from each patient in the intervention room by a trained study nurse (SK): each one before and after groin disinfection with alcoholic solution of povidone-iodine (Betaseptic®, Mundipharma, Switzerland, containing povidone-iodine 32.4mg, 389mg isopropanol and 389mg ethanol per ml). Groin swabs were taken in a defined skin area (25cm^2), which was standardized by a template as previously shown [15]. The template area was swabbed with a saline premoistened sterile cotton swab in a rotating motion. Each swab was immediately placed in a vial containing 2ml of a disinfection neutralizing solution, to avoid carry over effects of residual disinfectant [16]. Samples were analysed within six hours in the local microbiological laboratory following validated culture

methods including identification by matrix-assisted laser desorption/ionization-time of flight mass-spectrometry (MALDI Biotyper®, Bruker Daltonics, Germany).

Continuous variables were compared using t-tests, categorical data by chi-square or Fisher's exact test as appropriate. Variables with p-values < 0.1 were entered in a multivariate logistic regression model using SPSS 28.01.0 (SPSS IBM Corp. Released 2021. IBM SPSS Statistics for Windows, Version 28.0. Armonk, NY: IBM Cor).

Results

During the study period, 300 patients were included, data of four patients were dropped because they had repeat interventions, five because of missing clinical and one because of missing microbiological data. Overall, 290 patients were analysed; 245 (84.5%) received coronary angiography via femoral access, 31 (10.7%) received TAVR, eight patients (2.8%) had RHC, five (1.7%) PFO closure, and one (0.3%) was treated with MitraClip®. Mean age was 70 years and 30% were female. Patients colonized with enterococci had a significantly higher body mass index (obese patients were 2.3 times more frequently colonized with enterococci) and more often were diabetic than those without enterococcal colonization (Table I). All other parameters were similar between the groups.

In 48 patients, enterococci were detected before disinfection, in three of them, enterococci were still cultured after disinfection, and in one *E. faecalis* was only detected after disinfection (Table II). Enterococcal prevalence was therefore 16.6% before and 1.4% after disinfection and was similar for the two intervention groups (i.e. coronary angiography and TAVR). *Staphylococcus lugdunensis* was more frequently isolated than *S. aureus* with 11.4% (4.1%) before and 6.6% (2.4%) after disinfection. Only three patients were colonized with *Pseudomonas aeruginosa* and ten patients with an *Acinetobacter* spp. - none of them identified as *A. baumannii* sensu strictu.

Discussion

Not only AHA, but also the American expert consensus document on TAVR, recommend routine pre-interventional antimicrobial prophylaxis with a cephalosporin to prevent TAVR-associated IE [13]. The high proportion of enteroccoci in groin swabs provides evidence to adapt this policy to a regimen covering for enterococci.

Enterococci account for up to one third of early TAVR-associated IE and 26-30% overall in the SwissTAVI registry as well as internationally reported [6, 7]. Therefore, colonization at the insertion site with enterococci, even after disinfection, could explain in part the source of infection of TAVR-associated IE, particularly in the early phase. AHA recently dropped the recommendation for antimicrobial prophylaxis before TAVR from evidence B (moderate quality) to C (limited data) in 2017 [8]. Cephalosporins used for prophylaxis – except for the fifth generation such as ceftobiprole and ceftaroline – lack activity against enterococci, potentially explaining the downsizing of the recommendation because of insufficient effect almost in one quarter of patients. Consequently, the high enterococcal prevalence in patients with TAVR-associated IE early after the intervention resulted in adapted pre-interventional prophylaxis recommendations to an enterococcal-active agent (e.g. amoxicillin/clavulanic acid or ampicillin/sulbactam in penicillin non-allergic patients, and vancomycin in case of allergy) by our group, which was endorsed by the International Society for Cardiovascular Infectious Diseases (ISCVID) [14]. As the risk of infection of other cardiological devices implanted by a transfemoral access, i.e. PFO closure or MitraClip®, is very low, and especially without association with enterococci, in our opinion there is no urgent need to adapt antimicrobial prophylaxis for these patients.

Skin disinfection was performed by the cardiologists under strict study conditions with supervision of a trained study nurse: Despite state-of-the-art disinfection with three

applications, four patients were still positive for enterococci afterwards. One can assume that under non-study conditions, the likelihood of surviving enterococci after disinfection is even higher. Enterococci are less susceptible to heat and disinfectants and survive longer in the environment than most other vegetative bacteria. The habitat of *S. lugdunensis* is the groin: They belong to the group of coagulase-negative staphylococci, but their clinical importance is similar to *S. aureus*. This underlines again the importance that antimicrobial prophylaxis must optimally cover gram-positive bacteria including *S. aureus*, *S. lugdunensis*, and enterococci. The current prophylaxis recommendation with cephalosporins fails to cover enterococci, but amoxicillin/clavulanic acid and ampicillin/sulbactam cover both enterococci and staphylococci.

As a study limitation we admit that only the prevalence of enterococcal colonisation in the groin was assessed, therefore no data on the incidence of TAVR-associated endocarditis according to the colonisation status was recorded. As colonisation is a dynamic process, routine assessment of the colonisation status of the groin before TAVR will not change our recommendation to include the coverage of enterococci in the periinterventional antimicrobial prophylaxis. In addition, the effectiveness of a local decolonisation for enterococci to prevent TAVR-associated IE has not been proven in a clinical trial. Fortunately, the incidence of TAVR-associated IE is very low precluding results from a clinical randomized trial comparing different prophylactic regimens.

Conclusion

Common enterococcal colonization of the groin coupled with frequently isolated enterococci from patients with TAVR-associated IE provide strong evidence to replace currently recommended antimicrobial prophylaxis with cephalosporins before TAVR with a compound that is active against enterococci.

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Declarations of interest: None

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Contribution: AC and AFW designed the study, DW and MD collected, and analyzed the data, AC, DW and AFW wrote the manuscript. StS, RJ and RF critically reviewed and approved the final version of the manuscript.

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Tables

Table I: Risk factors for inguinal colonization with enterococci

	Enterococci cultured prior to cardiology intervention (n=49)	**No enterococci cultured prior to cardiology intervention (n=241)**	**p-value**	**Adjusted p-value**
Characteristic				
Age, mean years (SD)	71.7 (10.2)	69.5 (11.5)	0.223	
Female sex, n (%)	15 (30.6)	73 (30.3)	1.00	
BMI, kg/m^2 (SD)	29.69 (6.2)	26.90 (4.3)	<0.001	0.002
Diabetes mellitus, n (%)	25 (51.0)	71 (29.5)	<0.001	0.06
Current smoking, n (%)	29 (59.2)	138 (57.3)	0.93	
Arterial hypertension, n (%)	38 (77.6)	192 (79.7)	0.89	
Coronary artery disease, n (%)	42 (85.7)	179 (74.3)	0.012	
Dementia, n (%)	0 (0)	5 (2.1)	0.67	
Immunosuppression, n (%)	3 (6.1)	5 (2.1)	0.27	
COPD, n (%)	6 (12.2)	25 (10.4)	0.89	
EuroSCORE (SD)	1.68 (0.95)	1.66 (0.90)	0.92	
Urinary catheter, n (%)	3 (6.1)	2 (0.8)	0.9	
Antimicrobial treatment at time of the intervention, n (%)	1 (2.0)	10 (4.1)	0.48	

TAVR[1] vs. coronary angiography, n (%)	9 (18.4)	36 (14.9)	0.67	
Haemoglobin, mean g/L (SD)	136.2 (22.9)	134.64 (18.8)	0.60	
Leucocyte count, mean G/L (SD)	7.91 (2.4)	8.05 (3.2)	0.77	
Thrombocyte count, mean G/L (SD)	224.2 (97.3)	222.6 (64.3)	0.89	
Albumin, mean g/L (SD)	36.1 (4.8)	36.89 (4.5)	0.99	
HbA1c, mean % (SD)	6.59 (1.12)	6.14 (1.19)	0.086	

Abbreviations: SD, standard deviation; BMI, body mass index; COPD, chronic obstructive pulmonary disease; EuroSCORE, scoring system predicting mortality of a patient during cardiac surgery; TAVR, transcatheter aortic valve replacement

[1] Includes also patients treated with MitraClip®, and patients receiving percutaneous closure of patent foramen ovale and right heart catheterization

Table II: Microbiological results of inguinal swabs in patients receiving cardiac interventions before and after disinfection

	Before disinfection **n = 290**	**After disinfection** **n = 290**
Staphylococcus aureus[1]	12 (4.1)	7 (2.4)
Staphylococcus lugdunensis	33 (11.4)	19 (6.6)
Coagulase-negative staphylococci	95 (32.8)[2]	148 (51.0)[5]
Enterococcus spp.	48 (16.6)[3]	4 (1.4)[6]
Skin flora	39 (13.4)[4]	28 (9.7)[7]
Escherichia coli	10 (3.4)	1 (0.3)
Klebsiella spp.	14 (4.8)[8]	1 (0.3)[12]
Pseudomonas spp.	6 (2.1)[9]	-
Acinetobacter spp.	10 (3.4)[10]	-
Other gram-negative bacilli	14 (4.8)[11]	1 (0.3)[13]

Results are presented in n (%). Due to the detection of multiple microorganisms in most patients, the sum may exceed total patient number and 100%

Abbreviations: TAVR, transcatheter aortic valve replacement; spp, species

[1] All isolates meticillin susceptible (MSSA)

[2] *S. epidermidis* (31), *S. hominis* (25), *S. haemolyticus* (22), *S. simulans* (6), and others

[3] *E. faecalis* (43), *E. faecium* (4) (no vancomycin-resistant isolates), *E. gallinarum* (1)

[4] *Corynebacterium* spp. (10), *Bacillus* spp. (9), *Moraxella* spp. (7), *Paracoccus* spp. (7), *Streptococcus* spp. (3), *Rothia* spp. (2), *Micrococcus* spp. (2), and others

[5] *S. epidermidis* (113), *S. hominis* (21), *S. haemolyticus* (10), *S. simulans* (5), and others

[6] *E faecalis* (4) (no vancomycin-resistant isolates)

[7] *Corynebacterium* spp. (18), *Micrococcus* spp. (4), *Dermabacter* spp. (4), *Brevibacterium* spp. (3), and others

[8] *K. pneumoniae* (7), *K. aerogenes* (5), *K. oxytoca* (2)

[9] *P. aeruginosa* (3), *P. non-aeruginosa* (3)

[10] *A. ursingii* (5), *A. pitii* (4), *A. parvus* (1)

[11] *Morganella morganii* (5), *Proteus mirabilis* (4), *Enterobacter cloacae* (2), *Citrobacter koseri* (1), *Serratia marcescens* (1), *Salmonella enterica* (1), *Stenotrophomonas maltophilia* (1)

[12] *K. aerogenes*

[13] *Raoultella ornithinolytica*