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Long-term Prognosis Following Vascular Graft Infection: A 10-Year Cohort Study

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Background. Vascular graft infection (VGI) remains a severe disease with high mortality and relapse rates. We performed a retrospective single-center cohort study to highlight factors associated with long-term all-cause mortality in patients with vascular graft infection.

Methods. All patients hospitalized in our facility over 10 years for VGI were included. VGI was defined by the presence of a vascular graft or an aortic stent graft (stent or fabric), associated with 2 criteria among clinical, biological, imaging, or microbiological elements in favor of VGI. The primary outcome was all-cause mortality. Empirical antibiotic therapy was considered as appropriate when all involved pathogens were susceptible in vitro to the antibiotics used. The surgical strategy was defined as nonoptimal when the graft was not removed in a late-onset surgery (>3 months) or no surgery was performed.

Results. One hundred forty-six patients were included. Empirical antibiotic therapy was administered in 98 (67%) patients and considered appropriate in 55 (56%) patients. Surgery was performed in 136 patients (96%) and considered as optimal in 106 (73%) patients. In multivariable analysis, appropriate empirical antibiotic therapy was associated with a lower probability of mortality (hazard ratio, 0.47 [95% confidence interval, .30–.79]; *P* = .002). Long-term survival did not differ according to whether the surgical strategy was considered optimal or not (log-rank = 0.66).

Conclusions. Appropriate empirical antibiotic therapy is a cornerstone of the management of VGI. Whenever possible, antibiotics must be associated with optimal surgical management. However, surgery could potentially be avoided in comorbid patients who are treated with appropriate antibiotics.

Keywords. appropriate empirical antibiotic therapy; fluoroquinolone; long-term prognosis; optimal infectious surgical strategy; vascular graft infection.

Vascular grafts have radically changed the prognosis of patients with vascular disease. However, these grafts have an associated risk of infection that are associated with high rates of morbidity (ranging from 10% to 30% [1]) and mortality (ranging from 15% to 75%, depending on the localization of the prosthesis [2]).

The treatment of these infections generally includes removal of the graft [3, 4] and antibiotic treatment [1, 4, 5]. However, graft removal is not always possible, in particular in patients with severe comorbidities. Some recent studies suggest that graft removal should be avoided in some situations [4, 6, 7],

especially in the first 3 months following graft implantation [8–11]. It may seem obvious that antibiotic therapy has to be appropriate, particularly in such cases. Nevertheless, and in spite of recent recommendations [12], the efficacy and required duration of antibiotic therapy have not yet been confirmed considering the scarcity of available data.

Most studies in the current literature focus on surgical management, and they are often limited by their population size (range, 43–143 patients [13, 14]). There is also a great disparity in management between studies. The main outcomes are most often in-hospital mortality, sometimes limited to the year following infection.

Considering these uncertainties and the paucity of available literature in this domain, there is a clear need for additional data. We thus conducted a retrospective study including all of the patients treated for a vascular graft infection (VGI) in the same university hospital over a 10-year period. Our aim was to highlight factors associated with the long-term survival of these patients (especially the role of empirical antibiotic therapy) and to evaluate the impact of a nonoptimal infectious surgical strategy.

METHODS

Study Design

Following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [15], we performed a retrospective single-center cohort study. All patients hospitalized in the Infectious Diseases Department or in the Vascular Surgery department of the Dijon University Hospital (France) between 1 January 2008 and 31 December 2017 and with a T82 code in their medical file (indicating a diagnosis of complication of prosthesis or implants and cardiac or vascular grafts) were screened using the French hospital discharge database (Programme de médicalisation des systèmes d'information [PMSI]). This program is an exhaustive, nationwide database that provides information on all hospitalizations from all French healthcare facilities (including public and private hospitalizations). Each discharge report provides information on diagnoses that are encoded as primary or secondary diagnoses according to the 10th edition of the *International Classification of Diseases* (*ICD-10*). Discharge reports are mandatory and serve as the basis for the funding of both for-profit and non-profit hospitals [16, 17].

Patients were included in the study if the presence of a vascular graft or an aortic stent graft (stent or fabric) was confirmed and if a VGI was identified. VGI was defined by the criteria proposed by FitzGerald et al [18] and used in several other studies [19, 20]. According to these criteria, VGI was confirmed by the presence of at least 2 of the 3 following criteria: (1) a positive blood culture or a positive deep sample for a highly virulent pathogen such as *Staphylococcus aureus*, or 2 blood cultures or positive intraoperative samples for a mild virulent pathogen (eg, *Staphylococcus epidermidis*, *Corynebacterium* species, or *Cutibacterium* species); (2) the presence of local (inflammation, localized pain, erythema, swelling, fistula, purulent discharge) or systemic (fever, chills) signs of VGI; or (3) the presence of biological (inflammatory syndrome) or radiological (presence of bubble, peripheral embolus, periprosthetic collection, false aneurysm on computed tomographic scan or positive positron emission tomographic scan or positive white blood cell scan) signs of VGI.

Since their physiopathology is unique and do not appear similar to that of VGI, patients were not included in the study if they had a peripheral vascular stent infection or a prosthetic hemodialysis graft infection such as GORE-TEX vascular grafts. Superficial VGIs, corresponding to stage 1 or 2 of the Samson classification [21] on the operative report, were also not included because we considered that these cases were cutaneous infections, since they did not involve vascular graft, strictly speaking.

Patient Consent Statement

According to French regulations, patients' written consent nor formal institutional review board approval was not required for this retrospective study on anonymous data.

Data Collection

For each patient included, the epidemiological, demographic, clinical, biological, radiological, and therapeutic data were collected from electronic medical records.

The following comorbidities were systematically collected: age, diabetes mellitus, heart failure, respiratory failure (defined as forced expiratory volume in 1 second <50% of normal theoretical values or partial pressure of oxygen <60 mm Hg according to the French Health Authority [22]), body mass index (obesity defined as BMI ≥30 kg/m²), neurocognitive impairment (from mild to severe), chronic kidney disease (defined as the presence of an estimated glomerular filtration rate <60 mL/minute/1.73 m² according to the Kidney Disease: Improving Global Outcomes [KDIGO] definition [23]), cirrhosis, active cancer (meaning cancer with or without metastasis but not in remission), and alcohol consumption.

The clinical signs of VGI were also collected on admission, including fever (defined as a temperature ≥38.3°C), erythema, fistula, pain, ischemia, scar dehiscence, neutrophil count, and C-reactive protein levels.

Vascular graft infections were classified according to Samson stage [21] using data from the surgical report and blood culture results.

Extracavitary vascular graft infection corresponded to VGI located at peripheral vessels according to the intraoperative findings on the operative report, or otherwise according to imaging in the absence of surgery. Thus, the infected material is located under the inguinal fold, such as iliofemoral, femoral-popliteal, femoral-femoral, axillofemoral, and femoral-tibial VGI. Intracavitary vascular graft infection corresponded only to VGI classified as intra-abdominal or thoracic [2] and thus an infection concerning only the aorta or only localized at the aorta. Regarding the particularity of aorto-bifemoral infections, it was considered an intracavitary infection if an extension of the infection was observed at the level of the aorta on the imaging or the operative report; otherwise, it was considered as an extracavitary infection.

In view of the literature, in which an early onset of infection is considered to be between 2 and 4 months following implantation, we defined VGI as "early onset" when occurring within the first 3 months after the surgery [2, 5, 7, 12].

Microbiological documentation was collected from blood cultures and intraoperative samples, or if none of them were performed or negative, from superficial wound samples if performed. Intraoperative samples were inoculated on standard medium and into a heart-brain liquid enrichment broth (Bio-Rad) that was incubated for 14 days and systematically subcultured on day 14. Isolated bacteria were identified according to standard laboratory procedures using biochemical identification or mass spectrometry (matrix-assisted laser desorption/ionization–time of flight, Bruker). When cultures were negative and patient had a previous antibiotics treatment, amplification of the universal 16S ribosomal RNA (rRNA) gene using polymerase chain reaction (PCR) was performed.

Multidrug-resistant bacteria was defined as the presence in blood cultures or intraoperative samples of methicillin-resistant *Staphylococcus* species, extended-spectrum β-lactamase enterobacteria, and multidrug-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii* [24].

The time elapsed from symptom onset to effective therapeutic management (first surgery linked to the VGI, or the beginning of antibiotic therapy in the absence of surgery) was also collected.

Both empirical (antibiotics before microbiological results) and definitive (antibiotics administered for a longer period of time during the management of the infection) antibiotic treatments were systematically collected.

Empirical antibiotic treatments were considered "appropriate" when all the involved pathogens cultured from blood and intraoperative samples (or when no cultures were performed or all of them negative, from superficial wound samples) were susceptible in vitro to at least 1 of the antibiotics used. For patients with a negative culture but positive 16S rRNA PCR, we referred to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) [25] to determine whether the antibiotic therapy was suitable or not. When no microbiological documentation was available, only a combination of a broad-spectrum antibiotic active on gram-negative bacilli (such as piperacillin-tazobactam or cefepime) and an effective antibiotic against methicillin-resistant *S aureus* (MRSA) was considered as appropriate (such as vancomycin or daptomycin) in view of the documentation found in the previous cohorts [2, 19, 26].

Empirical antibiotics were considered "optimal" when all of the involved pathogens were susceptible in vitro to at least 1 of the antibiotics in the regimen AND if the antibiotic treatment was the first choice according to recommendations of the French Infectious Disease Society and/or the European Society of Clinical Microbiology and Infectious Disease, established according to microbiological documentation frequently found in vitro but also according to pharmacokinetic and pharmacodynamic parameters (in particular the action on the biofilm), the risk of toxicity, and providing the correct dosages. When the patient had no empirical antibiotics during management, this was considered as a nonappropriate and a nonoptimal empirical antibiotic.

Surgical management was classified into 4 categories: (1) in situ surgery (graft replacement in a single operative step, with implantation of the new prosthesis at the infection site); (2) extra-anatomical surgery (change of the prosthesis with implantation of a new prosthesis away from the site of infection); (3) conservative surgery (surgical debridement of the infected prosthesis without removing it); and (4) surgical removal alone (removal of the infected prosthesis without implantation of a new prosthesis) [7, 27].

In view of the literature and from an infectious point of view, the surgical strategy was defined as "nonoptimal" when the vascular graft was not removed in case of a late-onset surgery (considered as graft implanted for <3 months, based on a recent study finding that graft preservation of graft implanted for <3 months was associated with excellent long-term limb salvage and mortality rate [8]), or when no surgery was performed [3].

Outcome

The primary outcome was in-hospital and out-of-hospital all-cause mortality at last available follow-up.

The secondary outcomes collected were as follows: (1) VGI-related in-hospital death (in-hospital death directly linked to VGI and its complications); (2) VGI-related relapse (appearance or persistence of clinical [fever, pain, local signs, fistula, erythema, scar disruption, ischemia, bleeding], radiological, or biological signs suggestive of VGI, justifying additional surgical treatment, regardless of the time elapsed from the initial infection); and (3) in-hospital and out-of-hospital all-cause short-time mortality, defined as the occurrence of death in the first 30 days after inclusion in the cohort.

All the outcomes were collected until 28 August 2020 from the electronic medical records, or from "avis-de-décès.net" [28] and "Libra memoria" [29], which are frequently updated French websites that contain all the death certificates published in the French press and includes 3 461 914 and 15 143 367 death certificates, respectively, since 2000.

Statistical Analyses

Continuous variables are presented as median and interquartile range (IQR). Categorical variables are presented as numbers and percentages. Continuous variables were compared using the Kruskal-Wallis test and categorical variables using the χ^2 test, Poisson regression, or Fisher exact test, when appropriate. Survival analysis was performed using Kaplan-Meier statistics, and groups are compared using the log-rank test.

To determine independent variables associated with prognosis, first a univariate analysis was performed to compare patient characteristics according to vital status on 28 August 2020. Then, a multivariable analysis with the Cox model was performed. To avoid α risk inflation, the analysis was adjusted on the 10 baseline variables that were clinically relevant and statistically linked to the principal outcome in univariate analysis with a *P* value < .2. Thus, variables significantly associated with the outcome but with a low occurrence were not taken into account, similar to variables whose association with prognosis was biased. Then a step-by-step descending model was performed manually, excluding nonstatistically relevant variables. A classification and regression tree analysis (CART) was performed to separate patients into different homogeneous risk groups and to determine predictors for survival. CART analysis was used to grow a decision tree using the Gini splitting function with a minimum size set at 10 and a *P* value of .05. Finally, we performed survival analysis using Kaplan-Meier statistics, and groups were

compared using the log-rank test. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated. Statistical analyses were performed using Stata software (StataCorp, College Station, Texas). A P value < .05 was considered significant.

RESULTS

A total of 872 patients with a PMSI code of T82 were hospitalized in the Dijon University Hospital Infectious Diseases Department or the Vascular Surgery Department between 1 January 2008 and 31 December 2017. After an in-depth analysis of the medical files, 146 (17%) patients were included in the final analysis (see flowchart in the Supplementary Data).

One hundred twenty-eight patients had an extracavitary infection and 18 had an intracavitary infection. Regarding these patients, 12 (67%) had an intra-abdominal VGI and 6 (13%) had an intrathoracic VGI. Twenty-one patients had an aortobifemoral graft infection, including 3 with damage to the aorta observed on imaging or during surgery, and considered as intracavitary infection. The main characteristics of the included patients are summarized in Table 1.

Blood cultures were performed for 96 patients (66%) with a positivity rate of 45% (43/96 blood cultures), and intraoperative samples were performed for 134 patients (92%) with a positivity rate of 83% (112/134 intraoperative samples). The microbiological features from blood culture and intraoperative sample are reported in Table 1. *Staphylococcus aureus* was the most frequently involved bacteria (26 of 43 [60%] positive blood cultures, 44 of 113 [39%] intraoperative positive cultures). Moreover, nearly one-third (14/44 [32%]) of isolated *S aureus* samples were resistant to methicillin (MRSA). Among the 49% of patients (66/134) who had intraoperative samples but who were not already on antibiotics, 86% had positive cultures (56/66), compared with 82% (56/68 positive cultures) among the patients who had antibiotic therapy prior to surgery (P = .9). Two patients had negative intraoperative cultures but positive 16S rRNA PCR. Only 20 patients (14%) had negative or not performed blood cultures and intraoperative samples. Nine of these 20 patients had no microbiological documentation at all when considering superficial wound samples.

The median time from symptom onset to management was 7.5 days (IQR, 1.7–27 days), and the median time from diagnosis to management was 1 day (IQR, 0–4 days).

Only 3 patients (2%) received no antibiotic treatment during all management. Antibiotic therapies are detailed in Table 1. Concerning these 143 patients who received antibiotics at some point during their management, empirical antibiotic therapy was used to treat 98 (67%) patients. Empirical treatment was considered appropriate in 55 (37%) patients, and optimal in 32 (22%) patients. The empirical association of piperacillin-tazobactam or cefepime associated with a specific anti-MRSA treatment (glycopeptide or daptomycin) was used for 13 patients (14%) and was always considered appropriate and optimal. Regimens of empirical antibiotic therapy are detailed in the Supplementary Data. Among the patients whose empirical antibiotic therapy was nonappropriate, 17 (40%) were infected with multidrug-resistant bacteria.

Based on available microbiological results, rifampicin was used as a definitive treatment in 39 patients (27%), and fluoroquinolone was used as definitive treatment for 51 patients (39%). Median duration of antibiotics was 5 weeks (IQR, 3–7 weeks), and median duration of antibiotics after surgery was similar, corresponding to 5 weeks (IQR, 3–7 weeks). Empirical antibiotic therapy represented a median of 13% (IQR, 0.7%–0.21%) of total antibiotic therapy duration. Surgery was performed in 134 (96%) patients, and 67 (50%) of them had the infected vascular graft removed (Table 1).

The median time between the infection and the last available follow-up was 2.2 years (minimum, 8 days; maximum, 12.3 years). On 28 August 2020, 63% of patients included (93 patients) had died from any cause (Kaplan-Meier survival curves are shown in Figure 1A).

In-hospital death attributable to VGI was identified in 20 (14%) patients. VGI-related relapse was observed in 47 (32%) patients with a median number of relapses of 1 (IQR, 1–2) and a median delay before relapse of 12 weeks (IQR, 7–52 weeks). Finally, 5 patients (3%) died in the first 30 days following the diagnosis. All of them had nonappropriate empirical antibiotics.

In univariate analysis, the only factor associated with all-cause mortality was age, whereas appropriate empirical antibiotic therapy was significantly associated with better long-term survival (Table 2; Kaplan-Meier survival curves in Figure 1B). In a subgroup analysis, appropriate empirical antibiotic therapy was not associated with the number of relapses, whether using the χ^2 method or Poisson regression (P = .9 and P = .5, respectively). To assess the impact of appropriate empirical antibiotics, we performed Kaplan-Meier survival curves stratified according to "appropriate" vs "not appropriate" antimicrobial therapy and excluded patient with early death (curve available in Figure 1C). There was a trend to significance with a log-rank test = 0.06 in favor to appropriate empirical antibiotics.

In multivariable analysis, the 9 following adjustment variables were included: age, time between symptoms and management, gram-negative bacilli on intraoperative culture, appropriate empirical antibiotic therapy, optimal empirical antibiotic therapy, antibiotic treatment duration, vascular graft removal, use of rifampicin as definitive treatment, and use of fluoroquinolone as definitive treatment.

Age remained independently associated with a higher risk of mortality (HR +1 year, 1.03 [95% CI, 1.01–1.05]; P = .007), whereas appropriate empirical antibiotic therapy was independently associated with a lower risk of all-cause mortality (HR, 0.48 [95% CI, .29–.80]; P = .005) (Table 2).

Table 1.   Clinical, Biological, and Microbiological Characteristics and Management of Patients Presenting With Vascular Graft Infection

Characteristic	Overall (N = 146)	Extracavitary (n = 128)	Intracavitary (n = 18)	Early-Onset (n = 72)	Late-Onset (n = 74)
Age, y, median (IQR)	68 (62–76)	68 (63–77)	67 (58–75)	70 (64–78)	66 (60–74)
Sex, male	114 (78)	101 (79)	13 (72)	55 (76)	59 (80)
Comorbidity					
Diabetes mellitus	33 (23)	30 (23)	3 (17)	17 (24)	16 (22)
Heart failure	29 (20)	27 (21)	2 (11)	15 (21)	14 (19)
Respiratory failure	24 (16)	22 (17)	2 (11)	14 (19)	10 (13)
BMI ≥30 kg/m²	11 (7)	11 (9)	0 (0)	6 (8)	5 (7)
Active cancer	19 (13)	18 (14)	1 (6)	8 (11)	10 (13)
Chronic kidney failure	22 (15)	20 (16)	2 (11)	10 (14)	10 (13)
Other past medical history					
Chronic alcohol abuse	23 (16)	20 (16)	3 (17)	14 (19)	9 (12)
Cognitive impairment (mild to severe)	5 (3)	4 (3)	1 (6)	4 (6)	1 (1)
Clinical signs at admission					
Fever	66 (46)	53 (41)	13 (72)	29 (40)	37 (50)
Fistula	39 (27)	35 (27)	4 (22)	25 (35)	14 (19)
Scar dehiscence	87 (59)	86 (67)	1 (6)	54 (75)	23 (31)
Erythema	49 (37)	46 (36)	3 (17)	27 (38)	22 (30)
Pain	43 (29)	37 (29)	5 (28)	16 (22)	27 (36)
Ischemia	15 (10)	14 (11)	1 (6)	9 (13)	6 (8)
Bleeding	24 (16)	19 (15)	5 (28)	9 (13)	15 (20)
Septic shock	9 (6)	6 (5)	3 (17)	4 (6)	5 (7)
Blood culture performed	96 (66)	78 (61)	18 (100)	48 (67)	48 (65)
Positive blood culture	43 (29)	31 (24)	12 (67)	21 (29)	22 (30)
Intraoperative sample realized	134 (92)	119 (93)	15 (83)	65 (90)	69 (93)
Positive intraoperative sample	113 (77)	99 (77)	14 (78)	54 (75)	59 (80)
Negative blood culture and intraoperative sample	20 (14)	20 (16)	0 (0)	11 (15)	9 (12)
Antibiotics during management	143 (98)	125 (98)	18 (100)	72 (100)	71 (96)
Empirical antibiotic therapy	98 (67)	88 (69)	10 (55)	54 (75)	44 (59)
Appropriate empirical antibiotics	55 (37)	50 (39)	5 (28)	27 (38)	28 (38)
Optimal empirical antibiotics	32 (22)	29 (23)	3 (17)	18 (25)	14 (19)
Median antibiotic duration, wk (IQR)	5 (3–8)	5 (3–7)	51 (5–15)	5 (3–7)	6 (3–9)
Surgery performed	134 (92)	120 (94)	14 (78)	66 (92)	68 (92)
Optimal infectious surgical strategy performed	106 (73)	95 (74)	11 (61)	66 (92)	40 (54)
Death from all causes	93 (64)	84 (66)	9 (50)	48 (67)	45 (61)
Death attributable to vascular graft infection	20 (14)	15 (12)	5 (28)	8 (11)	12 (16)
Relapse	47 (32)	43 (33)	4 (22)	22 (31)	25 (34)
Blood culture identification	Overall (n = 43)	Overall (n = 31)	Overall (n = 12)	Overall (n = 21)	Overall (n = 22)
Staphylococcus aureus	26 (60)	21 (69)	5 (38)	12 (57)	14 (64)
Dnase-negative *Staphylococcus*	3 (7)	2 (6)	1 (8)	1 (5)	2 (10)
Streptococcus spp	3 (7)	2 (6)	1 (8)	0 (0)	3 (14)
Enterococcus spp	1 (2)	1 (3)	0 (0)	1 (5)	0 (0)
Pseudomonas aeruginosa	2 (5)	0 (0)	2 (15)	1 (5)	1 (4)
Enterobacteria	6 (14)	3 (10)	3 (23)	4 (19)	2 (10)
Fungal	2 (5)	2 (6)	0 (0)	2 (10)	0 (0)
Intraoperative culture identification	Overall (n = 113)	Overall (n = 99)	Overall (n = 14)	Overall (n = 54)	Overall (n = 59)
Staphylococcus aureus	44 (39)	40 (40)	4 (29)	18 (33)	26 (44)
Dnase-negative *Staphylococcus*	8 (7)	8 (8)	0 (0)	3 (5)	5 (8)
Streptococcus spp	4 (4)	3 (3)	1 (7)	1 (2)	3 (5)
Enterococcus spp	4 (4)	4 (4)	0 (0)	2 (4)	2 (3)
Pseudomonas aeruginosa	6 (7)	4 (4)	2 (14)	3 (5)	3 (5)
Enterobacteria	13 (12)	12 (12)	1 (7)	8 (15)	5 (8)
Anaerobia	4 (1)	2 (2)	2 (14)	1 (2)	3 (5)
Fungal	1 (1)	1 (1)	0 (0)	1 (2)	1 (2)

Table 1. Continued

Characteristic	Overall (N = 146)	Extracavitary (n = 128)	Intracavitary (n = 18)	Early-Onset (n = 72)	Late-Onset (n = 74)
Polymicrobial	28 (25)	24 (24)	4 (29)	18 (33)	10 (17)
Other	1 (1)	1 (1)	0 (0)	0 (0)	1 (2)
Multidrug-resistant bacteria	Overall (n = 40)	Overall (n = 37)	Overall (n = 3)	Overall (n = 26)	Overall (n = 14)
MRSA	14 (35)	14 (38)	0 (0)	10 (38)	4 (28)
MR-CoNS	3 (7)	3 (8)	0 (0)	1 (4)	2 (14)
MDR gram-negative bacilli	23 (57)	20 (54)	3 (100)	15 (58)	8 (57)
Empirical antibiotic therapy	Overall (n = 98)	Overall (n = 88)	Overall (n = 10)	Overall (n = 54)	Overall (n = 44)
Dual empirical antibiotic therapy	44 (45)	39 (44)	6 (60)	26 (36)	18 (41)
Large-spectrum β-lactam + MRSA treatment	17 (17)	14 (16)	3 (30)	6 (11)	11 (25)
Monotherapy empirical antibiotic therapy	51 (52)	47 (54)	4 (40)	28 (52)	23 (52)
Ampicillin + clavulanate alone	28 (28)	28 (32)	0 (0)	17 (31)	11 (25)
Definitive antibiotic therapy	Overall (n = 143)	Overall (n = 125)	Overall (n = 18)	Overall (n = 72)	Overall (n = 71)
Culture-based antibiotics treatment	126 (88)	108 (86)	18 (100)	66 (92)	60 (84)
Use of rifampicin alone or in combination as definitive treatment	39 (27)	32 (26)	7 (39)	17 (24)	22 (31)
Use of fluoroquinolone alone or in combination as definitive treatment	51 (36)	44 (35)	7 (39)	23 (32)	28 (39)
Type of surgery	Overall (n = 134)	Overall (n = 94)	Overall (n = 14)	Overall (n = 66)	Overall (n = 68)
Conservative surgery	67 (50)	61 (65)	6 (43)	39 (59)	28 (41)
In situ surgery	35 (26)	28 (30)	7 (50)	18 (27)	17 (25)
Extra-anatomical surgery	16 (12)	15 (16)	1 (7)	5 (7)	11 (16)
Surgical removal alone	16 (12)	16 (17)	0 (0)	4 (6)	12 (18)

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: BMI, body mass index; IQR, interquartile range; MDR, multidrug-resistant; MR-CoNS, Methicillin-resistant coagulase-negative staphylococci; MRSA, methicillin-resistant *Staphylococcus aureus*.

In CART analysis, using the same adjustment variables as in the logistic regression, for patients younger than 81 years, the next most important predictor was treatment with an appropriate empirical antibiotic. Finally, for these patients aged <81 years and who did not have appropriate empirical antibiotic therapy, the most important factor was the use of fluoroquinolone as definitive treatment (Figure 2).

Forty patients (27%) had a nonoptimal infectious surgical strategy (12 had no surgery and 28 underwent only a conservative surgery despite developing a late-onset VGI). Patients in whom the surgical strategy was nonoptimal from an infectious point of view had significantly more comorbidities and later-onset VGI, but death and relapse rates did not significantly differ from patients with an optimal infectious surgical strategy (P = .75 and P = .52, respectively; Table 3).

Survival was also not significantly different between these 2 groups (log-rank = 0.46) (Figure 3).

DISCUSSION

This large monocentric study on 146 patients hospitalized for VGI (using a strict definition) over a 10-year period, and with a long follow-up time (up to 12 years), confirms that VGI is a severe disease that is associated with a high mortality rate from all causes (64%) and VGI-related causes (14%). These rates are similar to those found in other studies (with all-cause death within 1 year of diagnosis ranging from 20% to 55% [5, 6] and with a mortality related to VGI within 30 days of diagnosis ranging from 10% to 25% [1, 19]). We have observed 32% of VGI-related relapse, which is quite similar to another study focusing on staphylococcal prosthetic VGIs and observing a VGI-related relapse rate of 25% [20].

The study highlights that administering an appropriate empirical antibiotic therapy is the most important modifiable factor associated with improved long-term survival. This phenomenon may seem surprising; however, it is already observed in prosthetic joint infection [30, 31]. In our work, empirical antibiotic therapy represented a median of 13% of the total antibiotic therapy duration, and this represents a significant part of the total duration of antibiotic therapy. It is likely that this initial antibiotic therapy is a key period, particularly because of establishment of the biofilm, which is set up very quickly. Thus, an inappropriate initial antibiotic therapy would not prevent the formation of biofilm, responsible for longer-term complications [32]. Focusing on mortality within the first 30 days after diagnosis, all patients had a nonappropriate empirical antibiotic treatment. However, in a subgroup analysis, appropriate empirical antibiotic therapy was not associated with the number of
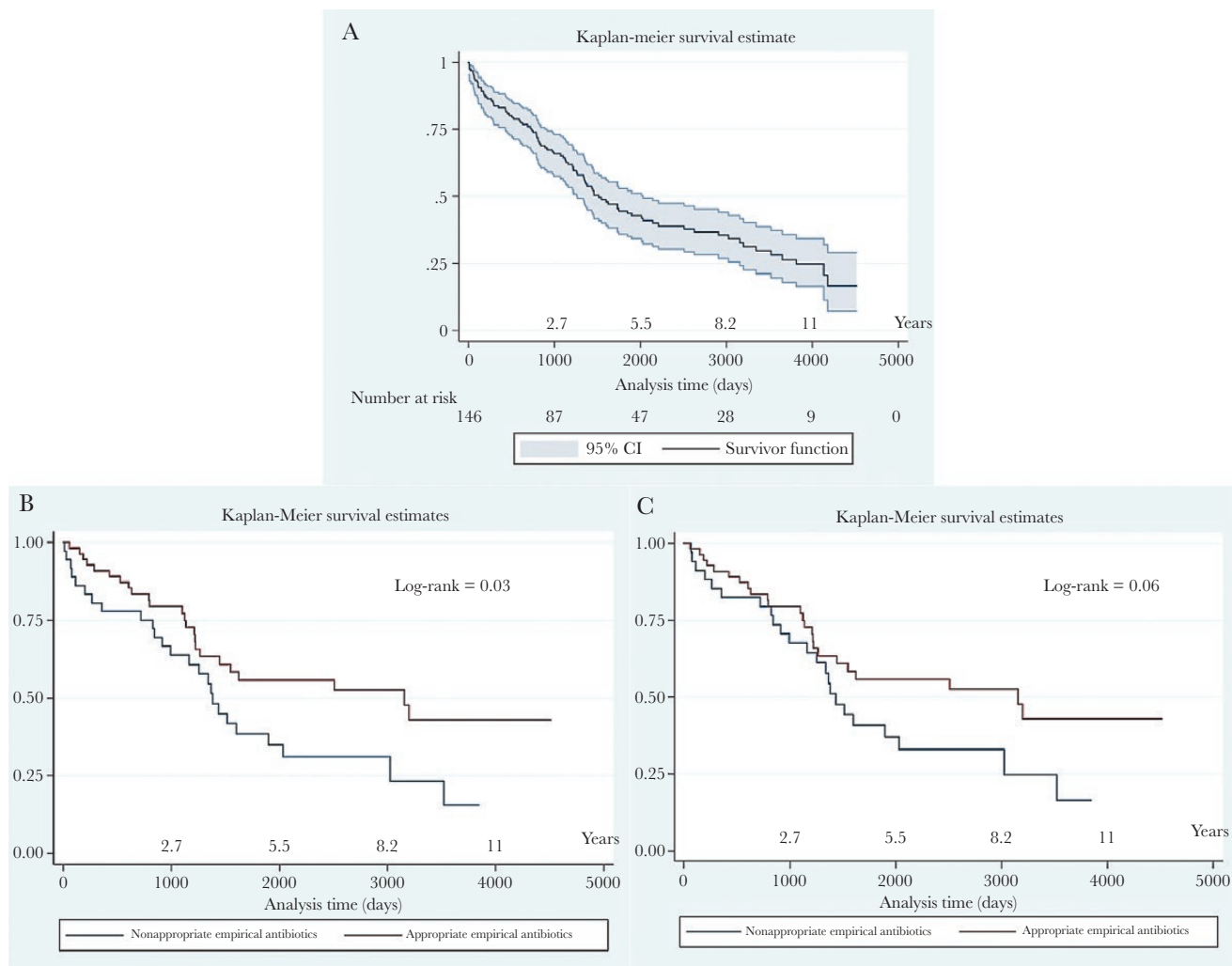
Figure 1. Survival curves of patients presenting with vascular graft infection (VGI) (*A*), patients presenting with VGI stratified by appropriate empirical antibiotics or not (*B*), and patients presenting with VGI stratified by appropriate empirical antibiotics or not and after excluding death within the 30 days after diagnosis (*C*). Abbreviation: CI, confidence interval.

relapses. This may suggest that more than antibiotic therapy, it may be surgery that could prevent relapse. Further testing for specific relapsing factors is needed.

To be appropriate, empirical antibiotic therapy has to be effective against all of the involved pathogens. In our study, *S aureus* was the most frequently found bacteria in blood cultures and intraoperative samples, which may be in a third of cases resistant to methicillin. This microbiological distribution is also observed in several other studies [14, 19, 33].

In light of these results, empirical treatment should be effective against MRSA. Daptomycin may thus be of interest, since it has been shown to prevent and eradicate biofilm in a subcutaneous rat pouch model of staphylococcal infection [34]. Moreover, high doses of daptomycin have been demonstrated to be safe [35], and daptomycin is associated with favorable outcomes in the treatment of VGI [36]. Considering that polymicrobial and multidrug-resistant gram-negative bacilli are often found

in VGI, as previously reported [26], anti-staphylococcal treatment has to be associated with a broad-spectrum antibiotic active against gram-negative bacilli (eg, piperacillin-tazobactam or cefepime). Unfortunately, few fungal species were found in our work, but they were not systematically the subject of testing.

Our data thus support the recent French recommendations suggesting the use of daptomycin in combination with piperacillin-tazobactam or cefepime as empirical antibiotic therapy [1, 12].

Since the administration of empirical antibiotic therapy was a key prognostic factor, our work raises the question of timing. Indeed, the positive impact of systematic antibiotic use could be counterbalanced by a lower likelihood of bacterial identification on samples if treatment is started before surgery. In a study by Legout et al [19], there was no difference in culture positivity between patients who did or did not receive antibiotic therapy 48 hours before surgery. For how long before surgery

Table 2. Univariate and Multivariable Analysis of Parameters Associated With All-Cause Mortality

Variable	HR	(95% CI)	P Value
Univariate analysis			
Age	1.03	(1.01–1.04)	.001
Diabetes	1.10	(.72–1.70)	.65
BMI ≥30 kg/m^2	0.87	(.47–1.59)	.64
Chronic kidney failure	1.51	(.88–2.60)	.13
Heart failure	1.23	(.74–2.03)	.41
Respiratory failure	1.33	(.80–2.24)	.27
Chronic alcohol abuse	1.02	(.61–1.70)	.93
Cognitive impairment (mild to severe)	2.11	(.91–4.94)	.08
Graft localization (intra-abdominal)	0.90	(.38–2.10)	.81
Septic shock	1.70	(.75–3.85)	.20
Leukocyte count	1.02	(.98–1.06)	.26
CRP level	1.00	(.99–1.00)	.97
Positive gram-positive cocci blood culture	0.98	(.57–1.70)	.95
Positive gram-negative bacilli blood culture	1.05	(.32–3.40)	.94
Positive intraoperative culture	0.71	(.41–1.24)	.23
Positive gram-positive cocci intraoperative culture	0.68	(.44–1.06)	.09
Positive gram-negative bacilli intraoperative culture	1.11	(.65–1.91)	.69
Multidrug-resistant bacteria identification	1.28	(.81–2.02)	.29
Time to infection (early)	1.02	(.68–1.53)	.91
Time between the onset of symptoms and management	0.99	(.99–1.00)	.14
Appropriate empirical antibiotic therapy	0.55	(.32–.96)	.03
Optimal empirical antibiotic therapy	0.64	(.34–1.21)	.17
Use of aminoglycoside in empirical antibiotics	0.75	(.37–1.55)	.44
Use of rifampicin for definitive treatment	1.00	(.63–1.58)	.99
Use of fluoroquinolone for definitive treatment	0.70	(.45–1.10)	.12
Antibiotic treatment duration (per week added)	0.84	(.84–1.18)	.12
Removal of infected graft	1.04	(.68–1.61)	.22
Optimal infectious surgical strategy	0.90	(.60–1.45)	.67
Relapse	0.84	(.56–1.29)	.44
After logistic procedure			
Age	1.03	(1.01–1.05)	.007
Appropriate empirical antibiotics	0.48	(.30–.80)	.003
Antibiotic treatment duration (per week added)	0.84	(.84–1.00)	.23

Abbreviations: BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; HR, hazard ratio.
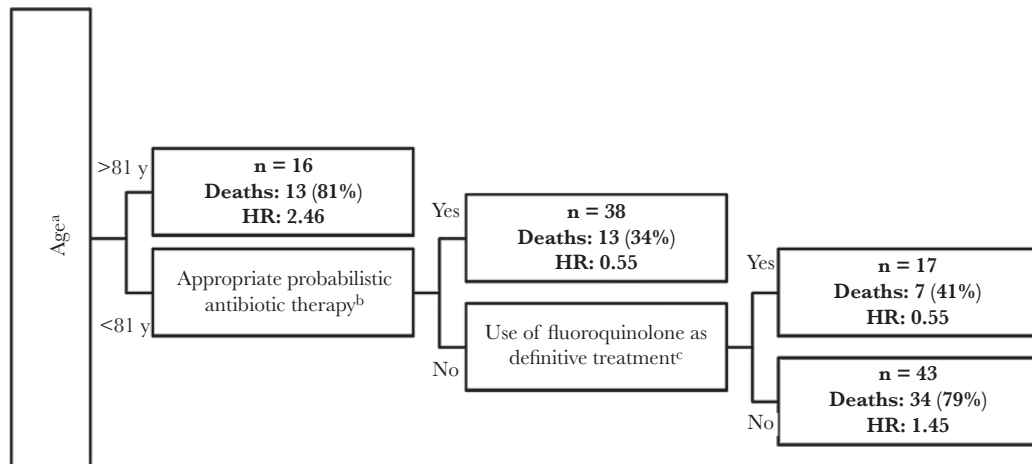

Figure 2. Classification and regression tree to predict mortality of patients with vascular graft infection. [a]For overall population, the most unfavorable factor is age >81 years (hazard ratio [HR], 2.46). [b]For patients <81 years, the most beneficial factor is appropriate empirical antibiotic therapy (HR, 0.55). [c]For patients aged <81 years without appropriate empirical antibiotic therapy, the most beneficial factor is the use of fluoroquinolone as definitive treatment (HR, 0.55).

Table 3. Clinical and Biological Characteristics, Treatment, and Outcomes of Patients With a Nonoptimal Infectious Surgical Strategy

Characteristic	Nonoptimal Infectious Surgical Strategy (n = 40)	Optimal Infectious Surgical Strategy (n = 106)	P Value
Age, y, median (IQR)	66 (59–77)	69 (63–76)	.46
Sex, male	30 (65)	84 (78)	.65
Comorbidity			
Diabetes mellitus	31 (78)	24 (23)	<.001
Heart failure	33 (83)	22 (21)	<.001
Respiratory failure	35 (88)	19 (18)	<.001
BMI ≥30 kg/m²	38 (95)	9 (8)	<.001
Active cancer	31 (78)	10 (9)	<.001
Chronic kidney failure	35 (88)	17 (16)	<.001
Other past medical history			
Chronic alcohol abuse	36 (90)	19 (18)	<.001
Cognitive impairment (mild to severe)	38 (95)	3 (3)	<.001
Onset of infection			<.001
Early	6 (15)	66 (62)	
Late	34 (85)	40 (38)	
Graft localization			.37
Extracavitary	33 (82)	95 (90)	
Intracavitary	7 (18)	11 (10)	
Blood culture performed	27 (44)	69 (65)	.006
Positive blood culture	12 (44)	32 (46)	1
Multidrug-resistant bacteria	8 (20)	32 (38)	.3
Empirical antibiotics	25 (62)	73 (69)	.3
Empirical appropriate antibiotics	15 (60)	40 (55)	.83
Use of rifampicin for culture-based treatment	11 (27)	28 (26)	1
Use of fluoroquinolone for culture-based treatment	11 (27)	40 (38)	.33
Suppressive antibiotic treatment	2 (5)	0 (0)	.07
Death from all causes	24 (60)	69 (65)	.75
Death attributable to vascular graft infection	7 (29)	14 (20)	.50
Relapse	15 (37)	32 (30)	.52

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: BMI, body mass index; IQR, interquartile range.
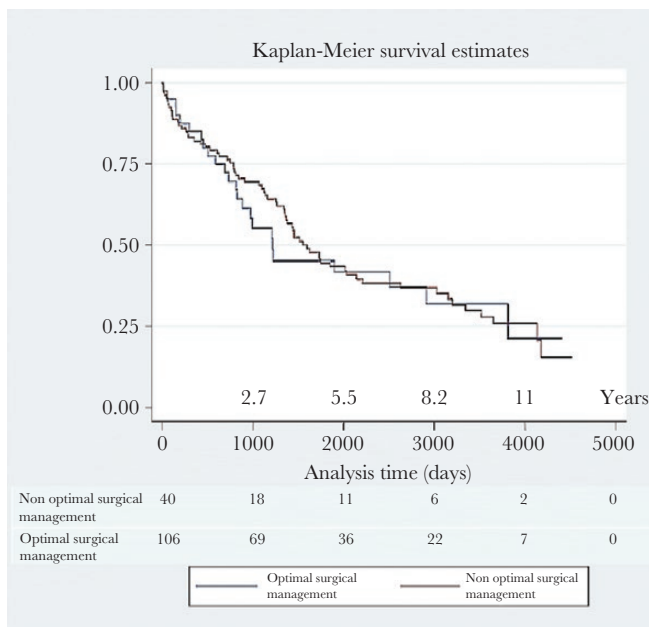
Figure 3. Survival curve of patients with an optimal infectious surgical strategy or not.

the antibiotics can be started without precluding microbial identification still has to be assessed.

Microbiological identification is of course valuable for choosing the final treatment. In our analyses, the use of fluoroquinolone as the definitive antibiotic therapy (use based on available microbiological identification and antibiotic susceptibility test in 94% of cases in our study) was the main positive factor for patients younger than 81 years who were not given appropriate empirical antibiotic therapy. This is probably linked to the fact that methicillin-sensitive *S aureus* (MSSA) and enterobacteria were the most frequently found pathogens in this work. Moreover, the use of rifampicin as culture-based definitive treatment has been shown to be associated with better survival in *S aureus* VGI [37].

Despite the possible risk of vascular aneurysm linked to fluoroquinolone [38], the association of rifampicin and fluoroquinolone could be preferred in proven cases of MSSA, and fluoroquinolone in proven cases of enterobacteria if possible, since the benefits seem greater in these infections with an appalling short-term prognosis. However, these results must be analyzed with care and cannot be generalized since these are specific to our center's population and our microbial epidemiology.

Though it remains a pivotal point for the management of VGI, surgery with graft removal was not associated with a better long-term prognosis in multivariable analysis. Moreover, survival was not significantly different between patients who had an optimal or nonoptimal infectious surgical strategy, albeit these patients were comparable in terms of important modifiable and nonmodifiable factors (age and antibiotic management). This was also observed in 2 other studies [6, 19].

By contrast, a recent study reported that graft removal was associated with better 1-year survival [14]. While this suggests that surgery has an impact in the first few years after infection, this early beneficial effect of surgery may be counterbalanced over time by the weight of patient comorbidities. We have to be cautious with these conclusions, especially since most of the participants with nonoptimal infectious surgical strategy had extracavitary infections that tend to be less severe and may not be representative.

Our study has limitations inherent to its retrospective design. Indeed, data were not collected for research; as a result, some charts are excluded due to the absence of certain crucial information, such as out-of-hospital mortality linked to VGI. On the top of that, since we have no formal linkage with other hospitals, it cannot be excluded that participants attended other institutions for care. However, we obtained a precise description of in- and out-of-hospital all-cause combined mortality following these infections, with no missing data thanks to the use of the 2 websites that contain all the death certificates published in the French press.

Regarding multivariable analysis, a possible immortal time bias could be present; however, the median delay between the start of the follow-up and the treatment initiation was 1 day and thus was considered as negligible in the analysis.

Moreover, we carried out a broad screening of patients who may have a VGI thanks to the use of PMSI database. Indeed, this is very complete because of the legal obligations of PMSI coding of hospital stays at discharge by the medical team combined with quality control of health insurance doctors. This database has already been used in several infectious diseases studies such as viral infection, bacterial infection, and vascular device infections [39–41].

Although we did not use the latest recommendations for the diagnosis of VGI [42] because our data collection started before they were published, we used a strict definition of VGI [18], as well as criteria already used in several previous studies [19, 20]. After additional analyses, all of the patients included in our study had a VGI according to the Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) classification, since all the criteria we have chosen correspond to the criteria of the MAGGIC classification.

To our knowledge, this is the first study of this size to assess the impact of empirical antibiotic therapy and optimal infectious surgical strategy during the management of VGI.

To conclude, it can be said that VGI remains a severe disease with high mortality and relapse rates. Appropriate empirical antibiotics remain a cornerstone of the management of VGI, and they must be effective against *S aureus* but also multidrug-resistant gram-negative bacilli. As often as possible, antibiotic treatment has to be associated with an optimal infectious surgical strategy; this allows for microbiological documentation and subsequent antibiotic adaptation. The use of fluoroquinolone as culture-based treatment looks promising when MSSA (preferably in association with rifampicin) or enterobacteria are found. Last, in certain situations, especially for patients with severe comorbidities, efficient antibiotic treatment may help circumvent surgery without causing excess long-term mortality, since long-term survival did not differ whether the surgical strategy was optimal or not from an infectious point of view.

Due to its retrospective design and the resulting biases, the results of this study cannot be generalized to the whole population and need to be strengthened by prospective multicenter studies.

Supplementary Data

Notes

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