Use of rifampicin and graft removal are associated with better outcomes in prosthetic vascular graft infection

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2 **Title page**

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Abstract:

Objectives: Prosthetic vascular graft infection (PVGI) is a very severe disease. We aimed to determine the factors associated with treatment failure.

Methods: Patients admitted to two University Hospitals with PVGI were included in this retrospective study. PVGI was classified as possible, probable or proven according to an original set of diagnostic criteria. We defined treatment failure if one of the following events occurred within the first year after PVGI diagnosis: death and infection recurrence due to the same or another pathogen.

Results: 112 patients were diagnosed with possible (n=26), probable (n=22) and proven (n=64) PVGI. Bacterial documentation was obtained for 81% of patients. The most frequently identified pathogen was *Staphylococcus aureus* (n=39). Surgery was performed in 96 patients (86%). Antibiotics were administered for more than 6 weeks in 41% of patients. Treatment failure occurred in 30 patients (27.5%). The factors associated with a lower probability of treatment failure were total removal of the infected graft (OR=0.2, 95% CI [0.1-0.6]), rifampicin administration (OR=0.3 [0.1–0.9]) and possible PVGI according to the GRIP criteria (OR=0.3 [0.1–0.9]).

Conclusions: Treatment failure occurred in 27.5% of patients with PVGI. Total removal of the infected graft and rifampicin administration were associated with better outcomes.

Introduction:

With a frequency estimated from 1% to 9% [1–4], prosthetic vascular graft infection (PVGI) is a rare complication of vascular surgery associated with severe consequences: the one-year mortality rate ranges from 19.0% to 34.4% [5–8], and limb amputation can exceed 40% of patients [9]. Despite this heavy clinical burden, many uncertainties still exist regarding the optimal management of this infection. PVGI diagnosis is sometimes hard to ascertain, as no well-defined diagnostic criteria exist. Hence, the conclusions of clinical studies can be biased if rigorous diagnostic criteria are not applied to include real PVGI patients. In addition, the available recommendations on PVGI therapy are only based on small case series and expert opinions [3,10–12]. Medical and surgical treatments should be combined guided by a multidisciplinary team, but little is known about the specific therapeutic modalities to apply. *In situ* reconstruction with or without graft removal is now thought to be the best surgical option and is the most frequently performed technique [5,13]. Proposals on the medical treatment of PVGIs have recently been published, highlighting the need of using molecules active against bacteria embedded inside the biofilm, but the authors regret the lack of solid evidence regarding antimicrobial therapy [11].

Thus, our study aimed to determine the occurrence of treatment failure in patients with PVGI in a large bicentric retrospective study by using a systematic diagnostic method. Secondly, we searched for factors associated with treatment failure in multivariate analysis.

Methods:

Ethics The Brest and Rennes ethics committees approved this observational study under reference numbers 2018CE.21 and 1585, respectively.

Inclusion All the patients treated for PVGI in the Brest University Hospital, France, between January 2011 and June 2016 or in the Rennes University Hospital, France, between January

2005 and December 2014 were included in this retrospective cohort study. Patients were identified using the French hospital discharge database. Patients with infection of a biological graft, a coronary graft or stent, a vascular patch, or a vascular endoprosthesis were excluded.

Definition of PVGI PVGI was defined according to the *Groupe de Réflexion sur les Infections de Prothèses Vasculaires* (GRIP) criteria [14], displayed in Table 1. Patients were classified according to the likelihood of PVGI: possible, probable or proven.

Outcome definition Treatment failure was a composite clinical criterion defined as the occurrence of one of the following events within the first year after PVGI diagnosis: death due to PVGI and infection recurrence due to the same or another pathogen during antimicrobial treatment or after treatment completion. Mortality due to PVGI was assessed by two independent physicians (MP, SP); in the case of disagreement, the opinion of a third physician was sought (RLB or MR). Treatment failure was diagnosed according to the GRIP criteria of PVGI at least 7 days after the initial PVGI diagnosis.

Statistical analysis Descriptive data were expressed as medians [25th–75th percentiles] for continuous variables and as numbers (percentages) for categorical variables. Factors were tested for association with treatment failure with non-parametric tests. Fisher's exact test was used for categorical variables, and the Wilcoxon rank sum test was used for continuous variables. Factors associated with treatment failure in univariate analysis ($p \leq 0.2$) were entered into a multivariate logistic regression model. Variable selection was performed using backward and forward selection ($p \leq 0.05$). Adjusted odds ratios were obtained with their 95% confidence interval [OR (95% CI)]. Analysis was performed using R statistical software, version 3.4.4 [15].

Results:

Population:

One hundred and twelve patients (81.3% men) were diagnosed with possible, probable and proven PVGI in 26 (23.2%), 22 (19.6%) and 64 cases (57.1%), respectively. Clinical characteristics and prognosis of patients according to the likelihood of PVGI are displayed in the supplementary table. Forty patients (35.7%) were treated at the Brest University Hospital, and 72 patients (64.3%) in Rennes. The median age was 66 [60-75] years (*Table 2*). The main cardiovascular risk factors were active smoking (84.3%) and arterial hypertension (60.7%). The two main comorbidities were coronary artery disease (42.0%) and chronic obstructive pulmonary disease (28.6%).

The site of infection was a peripheral (n=69), an aorto-thoracic (n=15), an aorto-abdominal (n=24) or an axillo-femoral (n=4) graft. Groin incision was performed at the time of graft implantation in 92 cases (81.4%). Thirty-one patients (27.7%) needed a second surgery for a postoperative non-infectious complication.

Diagnosis was made after a median time of 51 [16-851] days after graft implantation. At the time of diagnosis, all patients but three (97.3%) presented with a clinical sign, mainly pain (65.9%) and fever (62.0%). The C-reactive protein level was >10 mg/L for 92.3% of patients. Leucocytes were >10 G/L for 67.1% of patients. A CT scan was performed in 58 patients (51.8%) and contributed to the diagnosis in 89.7% of cases, whereas Doppler was performed in 15 patients (13.4%) and contributed to diagnosis in 80.0% of cases. Patients with aortic PVGI presented more frequently with fever than patients with peripheral PVGI (78.6% vs 51.5%, $p<0.01$) and less frequently with local erythema (34.3% vs 65.0%, $p<0.01$).

Infections were microbiologically documented in 91 patients (81.3%), including 37 patients with polymicrobial infection (40.7%). Among patients undergoing surgery with intraoperative bacterial sampling (n=92), 71 (77.2%) had a positive bacterial culture. Blood culture was performed in 53 patients (47.3%), and 33 (62.3%) cultures yielded a positive result. One infection due to *Coxiella burnetii* was documented with positive serology. The most frequent pathogens are displayed in Table 3 and were gram-positive cocci (62.5%), including

Staphylococcus aureus (27.3%) and *Enterococcus sp.* (14.6%); gram-negative bacilli (26.4%); and anaerobes (7.7%). The anatomical site of the PVGI did not influence the spectrum of infecting agents and patients with polymicrobial infections did not suffer more frequently from postoperative wound healing disorders than patients with monomicrobial infections.

Treatment:

All patients received antimicrobial therapy. Empirical treatment was given to 76 patients (67.9%), usually a beta-lactam, with an adjunct of an anti-MRSA agent in 46 patients (60.5%). Twenty-seven patients received antibacterial therapy before intraoperative bacterial sampling for a median duration of 6 [3-14] days. Receiving more than 7 days of antimicrobial treatment before surgery was associated with negative bacterial culture of intraoperative sampling (OR=2.44, p=0.02). This effect was not observed for shorter preoperative treatment durations. The remaining 36 patients were given culture-guided antibiotic therapy directly.

A rifampicin combination was used for definite therapy in 31 patients (27.7%), among whom 21 were infected with *S. aureus*, 7 with coagulase negative staphylococci, 1 with *Mycobacterium bovis* and 2 with a non-documented infection. The median treatment duration was 6 [6-9] weeks. Antibiotics were administered for at least 4 weeks in 84 patients (82.6%). Forty patients (40.8%) received antibiotic therapy for more than 6 weeks, including 8 patients (7.1%) receiving suppressive lifelong antimicrobial therapy.

Surgical treatment was performed in 96 patients (85.7%). Thirty-eight (33.9%) and ten patients (8.9%) required a second and a third surgery, respectively. The median time between the diagnosis of PVGI and the first surgery was 1 [0-6] day. Microbiological optimal surgery (*i.e.*, total removal of the infected prosthesis) was performed in 48 patients (42.9%). Reconstruction was needed in 60 patients and was performed with an allograft in 20 cases (20/60, 33.3%), an autologous vein in 22 cases (22/60, 36.7%) and prosthetic material in the remaining 18 patients. Five patients were treated initially with an endoprosthesis; two of those patients

required another surgery for total replacement with an allograft. Limb amputation was performed in 18 cases (16.8%).

The factors associated with optimal surgery in univariate analysis were peripheral-arterial PVGI vs abdomino-thoracic PVGI (47.9% vs 16.7%, $p=0.02$), age (63 vs 66 years old, $p<0.01$), and year of diagnosis ($p=0.01$). Patients diagnosed with PVGI after 2013 were more likely to undergo the optimal surgery than patients diagnosed in 2013 or before (56.4% vs 35.6%, $p=0.04$). All-cause mortality did not differ significantly between patients with microbiological optimal and microbiological non-optimal surgery.

Outcome:

All patients but one were followed for more than one year. Three patients (2.7%) and 25 patients (22.3%) died during the first 30 days and the first year after PVGI diagnosis, respectively. There were no intraoperative deaths.

Treatment failure occurred in 30 patients (27.5%) at one year of follow-up. Death due to PVGI occurred in 12 patients (10.7%), including 3 patients with infection recurrence. Twenty-two patients (19.6%) presented with infection recurrence that occurred before treatment completion in 13 cases. For 6 patients (5.4%), infection recurrence was due to another microorganism and for 15 patients (13.4%) to the same pathogen. The remaining patient successively presented with these two events. The all-cause mortality rate at one year was higher in patients with treatment failure (53.3% vs 10.1%, $p<0.01$).

According to univariate analysis, the factors significantly associated with a lower risk of treatment failure were microbiological optimal surgery (Figure), rifampicin administration and PVGI diagnostic probability as possible vs certain or probable according to the GRIP criteria (Table 4). No microbiological data were associated with treatment failure.

All three factors remained independently associated with a lower risk of treatment failure in the multivariate analysis: microbiological optimal surgery (OR=0.22 [0.07–0.57], $p<0.01$), possible PVGI according to the GRIP criteria compared to probable and proven PVGI (OR=0.27 [0.07–0.85], $p=0.04$), and rifampicin administration (OR=0.30 [0.09–0.87], $p=0.04$). As the diagnosis of PVGI for the patients classified in the “possible” group could be uncertain, we performed another multivariate analysis including only the patients with probable or proven PVGI: microbiological optimal surgery and rifampicin administration remained significantly associated with a better outcome.

Discussion:

Important information comes from this large bicentric retrospective study: i) treatment failure occurred in 27.5% of 112 patients and was associated with a high mortality rate of 53.3% at one year; ii) use of a rifampicin-combined regimen was associated with a better outcome; and iii) removal of the entire infected material also.

The lack of clear validated diagnostic criteria to define PVGI represents one of the most problematic issues for improving patient management and literature analysis. In a pioneering study published in 2005, Fitzgerald *et al* argued for a provisional set of diagnostic criteria, such as the Duke criteria used for infective endocarditis [12], and an English group of investigators also recently advocated for this [16]. However, to the best of our knowledge, no study on PVGI using this kind of diagnostic method has been published so far, and the results of previous studies can therefore be questioned. We based our work on the diagnostic criteria proposed by a French multidisciplinary expert group (GRIP) [14] to improve the diagnostic accuracy. We included all the patients considered to have a PVGI by their treating physicians and then, we classified all the patients according to the GRIP criteria. PVGI diagnosis likelihood is very high for patients classified as probable and proven PVGI, but quite low for patients with possible PVGI. Besides, treatment failure occurred more frequently in patients diagnosed with proven

and probable PVGI than in patients with possible PVGI. Our study reflects the real life: due to the severity of the disease, some patients are treated for PVGI even if the diagnosis is not confirmed. However, our results corroborate the GRIP classification according to diagnostic probability, and we hope that this systematic method could help physicians to manage this hard-to-treat infection.

We confirmed that PVGI is a very severe infection, with more than 27% of patients with treatment failure and an all-cause mortality rate of 22% at one year. Our treatment failure rate is similar to that of previous reports [5,17,18]. PVGI management relies on a multidisciplinary approach and requires antibiotic therapy associated with surgical procedures. The best antimicrobial agents and duration of antibiotic therapy for PVGI remain unknown. Most of our patients were initially treated with a high dosage of intravenous beta-lactam agents as recommended [11]. It was impossible to capture the impact of the different initial therapeutic options; surgical procedures probably had an initial greater impact than antibiotic treatment, but we found that the use of rifampicin was associated with a better outcome. This has already been demonstrated for joint-prosthesis infection [19] and for PVGI [5,17]. Rifampicin offers many advantages in difficult-to-treat infections: high biodisponibility, a large diffusion capacity, a large spectrum on gram-positive cocci, intense bactericidal activity even on intracellular bacteria [20], and on bacteria with altered metabolic state inside the biofilm [21,22]. In our work, the rifampicin effect was not differentiated according to the causative pathogen because of the small sample size. However, rifampicin was essentially used for *S. aureus* PVGI, and our results add another building block for its importance in material-related *S. aureus* infections.

One other question regarding the treatment of PVGI refers to the duration of antibiotic therapy. Available data only come from non-comparative studies whose objectives were not the evaluation of treatment duration. Most of those publications report 6 or 12 weeks of treatment, but others report shorter or longer antibiotic therapy. In our study, most patients received antibiotics for 6 weeks, regardless of whether the surgical treatment was optimal. The survival

and treatment failure rates were similar to those of other cohorts, and we did not find any impact of treatment duration on treatment failure. Thus, 6-week-long treatment seem to be long enough for PVGI.

A negative effect of more than 7 days of preoperative antimicrobial therapy was found on the bacterial growth of intraoperative samples. This effect was not observed for shorter treatments but could be different according to the pathogens and antimicrobial drugs. To minimize the risk of perioperative sample culture negativity, preoperative antibiotic therapy should be reserved for patients with sepsis.

Several techniques have been proposed for the surgical treatment of PVGI. Similar to osteo-articular infection, total removal of the entire infected graft is encouraged [3,23]. This statement is supported by little proof [7,24], and some studies have not found this positive impact [5], sometimes even demonstrating a negative effect [25]. Our study supports the need for this microbiological optimal surgical treatment in multivariate analysis. However, complete graft excision is not always possible or can be associated with poor functional results. The choice of surgical treatment may be guided by the operability of the patient and therefore may be correlated with the risk of mortality and induced morbidity. In our study, 85.7% of patients underwent surgery, and 42.9% of patients underwent microbiological optimal surgery with total removal of the infected vascular prosthesis. Most recent studies reported complete excision of the infected prosthetic vascular graft in 22.9% to 85.5% of cases [5–7,18]. In our study, microbiological optimal surgery was more frequently performed in young patients with peripheral-arterial surgery but did not depend on one specific comorbidity. The surgical rates increased every year. One explanation for this increasing rate is the recent improvements in surgical techniques and in anaesthesiology. Performing optimal surgery is now an option in patients who would have been previously recused. Second, in both participating centres, a multidisciplinary team that included infectious disease clinicians, surgeons and bacteriologists was established during the study period.

There were several limitations in this study. First, this was a retrospective study with all the associated limitations. However, we used a recognized definition of PVGI using criteria systematically recorded when taking care of patients with PVGI. Thus, we only included patients with a high probability of PVGI. In addition, missing data were very rare, and we were able to collect one-year follow-up data for all the patients except one. Moreover, due to the scarcity of the disease and the vast heterogeneity of patients, it is very difficult to conduct prospective multicentre studies in this field. Retrospective cohort studies such as ours are probably the least incorrect option to improve our knowledge about this very severe disease. Second, this study included patients with various surgical and medical approaches, but this reflects the vast heterogeneity of PVGI patient management. We aimed to describe the classic care of patients with PVGI in real life to draw interesting conclusions in daily practice.

Conclusion:

In conclusion, PVGI, a biofilm-associated infection, is associated with a high risk of treatment failure. In this retrospective study, complete excision of the infected graft and rifampicin administration were associated with favourable outcomes. As complete excision of the graft constitutes a major surgery, PVGI diagnosis should be based on a recognized definition. Our study demonstrated the reliability of the GRIP criteria for diagnosis. Prospective studies using such a definition of PVGI are needed to clarify the best PVGI management choices.

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1 **Tables:**2 **Table 1. *Groupe de Réflexion sur les Infections de Prothèses Vasculaires (GRIP)* diagnostic criteria**

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Proven PVGI:
Two criteria among the following are required: <ul style="list-style-type: none"> • positive smear or culture of intra-operative samples of the vascular prosthesis or periprosthetic tissues • periprosthetic suppuration • presence of collections or periprosthetic air bubbles after eight postoperative weeks • vascular prosthesis exposition through wound or gut
Probable PVGI:
Two clinical criteria among the following are required: <ul style="list-style-type: none"> • fever, shaking chills, septic shock, or haemorrhagic shock due to aorto-digestive fistula or anastomotic rupture of the bypass • local pain • erythema • local tumefaction • suppurative fistula • abscess or lack of vascular material integration (except PTFE implant) And a microbiological criterion: <ul style="list-style-type: none"> • one positive blood culture • if commensal flora bacteria are isolated, two positive haemocultures are required Or a radiological criterion: <ul style="list-style-type: none"> • presence or persistence of collection and/or periprosthetic air bubbles after 8 postoperative weeks • abscess • false aneurysm
Possible PVGI:
One criterion among the following is required <ul style="list-style-type: none"> • a clinical criterion (as listed above) • a biological criterion: C-reactive protein level more than 10 mg/L and/or hyperleukocytosis more than 10 g/L • a radiological criterion (as listed above)

Table 2. Population characteristics

Characteristics	Treatment success (n=82)	Treatment failure (n=30)	Total (n=112)
Men, <i>n</i> (%)	68 (82.9)	23 (77.7)	91 (81.3)
Age (years), <i>median</i> [IQ1-IQ2]	65 [59-73]	67 [61-78]	66 [60-75]
Diabetes mellitus, <i>n</i> (%)	18 (22.0)	10 (33.3)	28 (25.0)
Chronic obstructive pulmonary disease, <i>n</i> (%)	23 (28.1)	9 (30.0)	32 (28.6)
Arterial hypertension, <i>n</i> (%)	49 (60.5)	19 (63.3)	68 (60.7)
Coronary artery disease, <i>n</i> (%)	33 (40.2)	14 (47.7)	47 (42.0)
Solid cancer, <i>n</i> (%)	20 (24.4)	5 (17.7)	25 (22.3)
Stroke, <i>n</i> (%)	13 (15.9)	2 (6.7)	15 (13.4)
Severe renal insufficiency, <i>n</i> (%)	15 (18.3)	7 (24.1)	22 (19.6)
Immunosuppression, <i>n</i> (%)	10 (12.2)	5 (16.7)	15 (13.4)
Active smoking, <i>n</i> (%)	56 (86.2)	19 (79)	75 (84.3)
Presentation at time of diagnosis			
Fever, <i>n</i> (%)	50/79 (63.3)	17/29 (58.6)	67/108 (62.1)
Local pain, <i>n</i> (%)	41/60 (68.3)	13/24 (59.1)	54/82 (65.9)
Local erythema, <i>n</i> (%)	37/70 (52.9)	14/25 (56.0)	51/95 (53.7)
Fistula or swelling, <i>n</i> (%)	40/76 (52.6)	17/28 (60.7)	57/104 (54.8)
Scar disunion, <i>n</i> (%)	35/76 (46.1)	9/25 (36.0)	44/101 (43.6)
White blood count > 10 G/L, <i>n</i> (%)	47/73 (64.4)	18/24 (75.0)	65/97 (67.0)
C-reactive protein > 10 mg/L, <i>n</i> (%)	38/42 (90.5)	15/15 (100)	53/59 (93.0)

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Table 3. Microbiological data

Bacterial documentation per patient	N (%)
Bacterial documentation	91/112
Polymicrobial PVGI	(81.3)
Positive preoperative samples	37/112
Positive blood samples	(33.0) 71/96
Microorganisms isolated (n=144)	144 (100)
Aerobic Gram-positive	90 (62.5)
Methicillin-sensitive <i>Staphylococcus aureus</i>	36 (25.0)
Methicillin-resistant <i>Staphylococcus aureus</i>	3 (2.1)
Coagulase-negative staphylococci	17 (11.8)
<i>Enterococcus sp.</i>	21 (14.6)
<i>Streptococcus sp.</i>	13 (9.0)
Aerobic Gram-negative bacilli	38 (26.4)
<i>Escherichia coli</i>	12 (8.3)
<i>Pseudomonas aeruginosa</i>	7 (4.9)
Various	19 (13.2)
Anaerobes	11 (7.7)
<i>Candida sp.</i>	1 (0.7)
<i>Others</i>	4 (2.8)

Table 4. Factors associated with poor outcome in univariate and multivariate analyses

	OR [95% CI]	p-value	OR [95% CI]	p-value
Optimal surgery	0.32	0.018	0.22 [0.07–0.57]	p<0.01
Rifampicin administration	[0.10-0.87] 0.41	0.1	0.30 [0.09–0.87]	0.04
Diagnostic probability (possible PVGI)	[0.11-1.27] 0.40	0.13	0.27 [0.07–0.85]	0.04
	[0.09-1.36]			

Supplementary table. Population characteristics according to GRIP definition of PVGI

Characteristics	Total (n=112)	Proven or probable PVGI (n=86)	Possible PVGI (n=26)	P-value
Men, <i>n</i> (%)	91 (81.3)	73 (84.9)	18 (69.2)	NS
Age (years), <i>median</i> [IQ1-IQ2]	66 [60-75]	66 [60-75]	61 [59-73]	<0.05
Diabetes mellitus, <i>n</i> (%)	28 (25.0)	24 (27.9)	4 (15.4)	NS
Chronic obstructive pulmonary disease, <i>n</i> (%)	32 (28.6)	23 (26.7)	9 (34.6)	NS
Arterial hypertension, <i>n</i> (%)	68 (60.7)	51 (60.0)	17 (65.4)	NS
Coronary artery disease, <i>n</i> (%)	47 (42.0)	38 (44.2)	9 (34.6)	NS
Solid cancer, <i>n</i> (%)	25 (22.3)	19 (22.1)	6 (23.1)	NS
Stroke, <i>n</i> (%)	15 (13.4)	14 (16.3)	1 (3.8)	NS
Severe renal insufficiency, <i>n</i> (%)	22 (19.6)	17 (20.0)	5 (19.2)	NS
Immunosuppression, <i>n</i> (%)	15 (13.4)	12 (14.0)	3 (11.5)	NS
Active smoking, <i>n</i> (%)	75 (84.3)	59 (83.1)	16 (88.9)	NS
Initial surgery				
Peripheral PVGI, <i>n</i> (%)	69 (61.6)	54 (62.8)	15 (57.7)	NS
Groin incision	92 (81.4)	70 (82.6)	21 (80.8)	NS
Presentation at time of diagnosis				
Fever, <i>n</i> (%)	67/108 (62.1)	54 (65.1)	13 (52.0)	NS
Local pain, <i>n</i> (%)	54/82 (65.9)	44 (65.7)	10 (66.7)	NS
Local erythema, <i>n</i> (%)	51/95 (53.7)	40 (54.1)	11 (52.4)	NS
Fistula or swelling, <i>n</i> (%)	57/104 (54.8)	47 (58.0)	10 (43.5)	NS
Scar disunion, <i>n</i> (%)	44/101 (43.6)	33 (42.3)	11 (47.8)	NS
White blood count > 10 G/L, <i>n</i> (%)	65/97 (67.0)	51 (68.0)	14 (63.6)	NS
C-reactive protein > 10 mg/L, <i>n</i> (%)	53/59 (93.0)	41 (93.2)	12 (92.3)	NS
Microbiological documentation, <i>n</i> (%)	91 (81.3)	78 (90.7)	13 (50)	<0.05
Polymicrobial infection, <i>n</i> (%)	37 (33.0)	30 (34.9)	7 (26.9)	NS
Treatment and outcome				
Rifampicin-based regimen, <i>n</i> (%)	31 (27.7)	25 (29.1)	6 (23.1)	NS
Antimicrobial therapy for 6 weeks or more, <i>n</i> (%)	40 (40.8)	32 (41.6)	8 (38.1)	NS
Optimal surgery, <i>n</i> (%)	48 (42.9)	41 (47.7)	7 (26.9)	NS
Death at one year, <i>n</i> (%)	25 (22.3)	20 (23.5)	5 (19.2)	NS
Treatment failure, <i>n</i> (%)	30 (27.5)	26 (31.3)	4 (15.4)	NS

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