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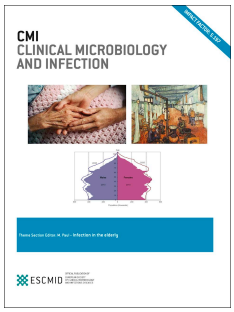

Suppressive antibiotic therapy in prosthetic joint infections: A multicentre cohort study

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Suppressive antibiotic therapy in prosthetic joint infections: A multicentre cohort study

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ABSTRACT

Objectives: To describe the effectiveness of suppressive antibiotic treatment (SAT) in routine clinical practice when used in situations in which removal of a prosthetic implant is considered essential for the eradication of an infection, and it cannot be performed. Materials/methods: This was a descriptive retrospective and multicentre cohort study of prosthetic joint infection (PJI) cases managed with SAT. SAT was considered to have failed if a fistula appeared or persisted, if debridement was necessary, if the prosthesis was removed due to persistence of the infection, or if uncontrolled symptoms were present. Results: In total, 302 patients were analysed. Two hundred and three of these patients (67.2%) received monotherapy. The most commonly used drugs were tetracyclines (39.7% of patients) (120/302) and cotrimoxazole (35.4% of patients) (107/302). SAT was considered successful in 58.6% (177/302) of the patients (median time administered, 36.5 months; IQR [20.75-59.25]). Infection was controlled in 50% of patients at five years according to Kaplan-Meier analysis. Resistance development was documented in 15 of 65 (23.1%) of the microbiologically documented cases. SAT failure was associated with age <70 years (sub-hazard ratio (SHR) 1.61, 95% CI [1.1-2.33]), aetiology other than gram-positive cocci (SHR 1.56, 95% CI [1.09-2.27]), and location of the prosthesis in the upper limb (SHR 2.4, 95% CI [1.5-3.84]). SAT suspension was necessary due to adverse effects in 17 of 302 patients (5.6%). Conclusions: SAT offers acceptable results for patients with PJI when surgical treatment is not performed or when it fails to eradicate the infection.

INTRODUCTION

Treatment of prosthetic joint infections (PJIs) aims to improve or preserve the function of the implant, prevent pain and eradicate the infection. Combined medical and surgical therapy is always necessary to eradicate infection(1). Removal of the implant is mandatory in chronic PJI(2) but acute PJIs can be managed by debridement, antibiotics and implant retention (DAIR)(3,4). Clinicians can, however, face situations in which surgical management, for

various reasons, is not optimal or does not occur, and therefore, the goal of eradicating the infection is abandoned. Thus, the option of using suppressive antibiotic therapy (SAT) without removing the prosthesis emerges. SAT can be defined as the indefinite administration of antibiotics with the objective of reducing the patient's symptoms and/or preventing progression of the infection. There was heterogeneity in previous studies about SAT, not only in the selection of patients but also in the criteria used to evaluate SAT success or failure. The reported success rates varied from 23.1% to 86.2%(5–8). In addition, the number of patients included was small, and information on the adverse effects of prolonged administration of antibiotics was not usually recorded. Overall, the efficacy of SAT and the factors that determine this efficacy, such as considerations related to the choice, dosage, and safety of the antibiotics used, are currently unknown.

The aim of our study was to describe the effectiveness of SAT in routine clinical practice when used in patients with chronic PJIs in whom the implant is not removed or in patients with acute PJIs after failure of the DAIR strategy; both are situations in which removal of the implant is considered essential for eradication of the infection. The secondary objectives of the study were to analyse the factors associated with failure of SAT and to evaluate its safety.

MATERIALS AND METHODS

This was a retrospective, multicentre, cohort study of patients with PJI who were managed with SAT. The study was conducted in 29 hospitals within the collaboration of the European Study Group of Implant-Associated Infection (ESGIAI) and the *Grupo de Estudio de Infección Osteoarticular* (GEIO). In every participating centre, the clinician expert in bone and joint infections was instructed to include all consecutive PJI cases managed by SAT that met the inclusion criteria. The observation period was from October 2003 to September 2016.

Patients were considered to have a PJI if at least one of the following conditions occurred: 1) a fistula communicating with the prosthesis; 2) local inflammatory signs together with elevated

C-reactive protein (CRP), radiological signs of infection and positive cultures; 3) synovial fluid count >4,300/mm^3 with >80% neutrophils (hip) or >1,100/mm^3 with >64% neutrophils (knee) in chronic infections(9,10); 4) the same microorganism was isolated from at least two samples of intraoperative cultures.

The PJIs were classified according to modified Tsukayama criteria(11). Briefly, the PJIs were classified as early postoperative (first three months after surgery), late chronic (symptoms not acute after three months), haematogenous (acute symptoms in a previously asymptomatic joint) and positive intraoperative culture (unsuspected septic loosening diagnosed during surgery) (Table S1, supplemental material). The inclusion criteria were as follows: 1) age over 18 years; 2) received SAT for a PJI in which a potentially curative surgical treatment had not been performed; and 3) follow-up of at least 6 months.

We defined SAT as the indefinite administration of antibiotics with a non-curative intention, in the context of either a PJI for which cure would require complete removal of the implant (as occurs for late chronic infections or an acute infection for which conservative treatment such as DAIR has failed).

SAT failure was indicated by the appearance or persistence of a fistula, the need for debridement or replacement of the prosthesis due to persistence of the infection, or the presence of uncontrolled symptoms. In cases in which none of these events occurred, the SAT was considered successful. Death was considered a SAT failure only if, in the opinion of the researcher, it was related to the PJI.

Epidemiological variables, the aetiology of the infections, the reason SAT was chosen, the type of surgery, the antibiotics used, the adverse effects and the clinical evolution until the last visit were collected. The information was recorded in a centralized electronic database. Qualitative variables were described as absolute and relative frequencies, while quantitative variables were described as the mean and standard deviation if the distribution was normal and as the median and interquartile range (IQR) if it was not. Quantitative variables were statistically analysed

using the Chi-squared test. To compare qualitative variables with quantitative variables, Student's t-test or ANOVA was performed according to the number of categories.

To evaluate the effect of SAT during and in the presence of competing events, the Fine-Gray competing risk regression model (1999) was used to estimate the sub-hazard ratio (SHR)(12,13). The variables that were clinically relevant and statistically significant in the univariate model were included in the multivariate model. Statistical significance was defined as $p<0.05$. Death was considered a competing event. To quantify the variability between hospitals, the median odds ratio (MOR) was calculated. This value indicates the median of the OR of SAT failure between two hospitals(14). The study was approved by the Ethics and Clinical Research Committee of the hospital with which the study coordinating team is associated.

RESULTS

A total of 340 patients with PJI participated in the study. Twenty-one cases were excluded due to insufficient or confounding data, and 17 cases were excluded because they did not meet the inclusion criteria. Therefore, 302 cases were finally analysed.

Table 1 presents a description of the patients, and Table 2 lists the microorganisms that were isolated. Most of the cultures were monomicrobial, although 41/302 patients (13.6%) had two or more microorganisms. The main reasons that non-curative surgical management was not performed were the decision of the surgeon in 82/302 cases (27.2%), high surgical risk in 80/302 cases (26.5%), advanced age in 71/302 cases (23.5%), the patient's decision in 70/302 cases (23.2%), the anticipation of poor functional results in 69/302 cases (22.8%), and the presence of minor symptoms in 35/302 cases (11.6%). In 157/302 patients (52.0%), several of these reasons occurred simultaneously.

SAT was administered for a median of 36.5 months (IQR [20.75-59.25]). For 17/302 patients (5.6%), the clinicians chose intermittent antibiotic administration with fixed antibiotic-free periods. Only 103/302 patients (34.1%) started SAT intravenously, and this practice was

performed regardless of age. Most patients (203/302 patients, 67.2%) underwent SAT regimens that used a single antibiotic, and 54/302 patients (17.9%) started with a combination regimen that was subsequently simplified to monotherapy. Thirty patients (9.9%) received a combination of antibiotics throughout SAT, and 15/302 patients (5.0%) started with a single antibiotic but later had a second drug added to their regimen due to lack of response.

The most commonly used oral antibiotics were tetracyclines, followed by cotrimoxazole. Figure 1 shows the mean and cumulative months of treatment per patient for each group of antibiotics. Seventy patients (23.2%) received rifampicin in combination with another antibiotic for a median of 3.8 months (IQR [1.9-12.0]).

SAT was considered successful in 177 patients (58.6%) and failed in 125 of 302 patients (41.4%). The most frequent reason for failure was a need to remove the prosthesis, which occurred 61 of 125 times (48.8%), followed by presence of a fistula in 31 patients (24.8%), need for debridement in 19 patients (15.2%), and poor symptom control in 14 patients (11.2%). Figure S1 (supplementary material) shows the patients' symptoms and CRP levels at the beginning of SAT and at the last follow-up for patients with successful SAT and for patients in whom SAT failed.

Ninety-two patients (30.5%) required hospitalization after initiating SAT for a cause related to the PJI. The median follow-up to a failure event or death was 25 months (IQR [12-40]). In total, 46/302 patients (15.2%) died during the follow-up period, none for a reason directly related to the PJI. Success rates of approximately 75% and 50% were observed at two years and five years, respectively (Figure 2). Thirty-four percent of the patients who experienced success received SAT for at least 4 years (Figure S2).

There was microbiological documentation of failure in 65 patients of 125 (52%). Among the possible causes for the failure of SAT, the reported causes were the suspension of SAT in 21/125 cases (16.8%), the development of resistance in 15 cases (of 65, 23.1% of microbiologically documented cases), the appearance of an unsuspected microorganism in 14

cases (of 65, 21.5% of microbiologically documented cases), and poor adherence to treatment in nine cases of 125 (7.2%). However, in 67/125 cases (53.6%), the cause of the SAT failure was unknown.

The univariate and multivariate risk factors for failure are shown in Table 3. Competing risk analysis showed that the following independent variables were associated with SAT failure: age younger than 70 years, aetiology other than gram-positive cocci, and location of the prosthesis in the upper limb. In the multilevel model, the MOR adjusted for the number of hospital beds was 1.5 (IOR (interval odds ratio)[1.2-2.8]). This variability did not change if the variable is included in the multivariate model (MOR 1.54). We found no relationship between the use of quinolones and success or failure in patients whose infections were due to GNB (SHR 0.77, 95% CI [0.33-1.80], p 0.55). Rifampicin use was not associated with success or failure of SAT in PJI due to GPC (SHR 1.13, 95% CI [0.25-5.16], p 0.88).

During the follow-up period, 104 adverse effects were recorded in 81/302 patients (26.8%); the majority of these were gastrointestinal (16.9%) and cutaneous (5.3%). Overall, 23 patients presented more than one adverse effect. However, SAT was suspended in only 17/302 patients (5.6%), while 46/302 (15.2%) changed antibiotics to avoid the adverse effect. Only three patients (1%) developed *Clostridium difficile* infection (Table S2, supplementary material).

DISCUSSION

In our study, the included patients suffered from a previously failed DAIR or an established chronic infection and lacked potentially curative surgical management. In this context, the probabilities of remaining infection-free at two years and five years are approximately 75% and 50%, respectively.

The efficacy of SAT was indirectly demonstrated by Byren *et al*. In their cohort study of patients with PJIs who were managed using DAIR and prolonged antibiotic therapy, the rate of failure was four times higher in patients who discontinued their antibiotic treatment than in the

remaining patients, regardless of whether the infection was acute or chronic(7). The success rates reported in various studies range from 23% to 86%. The studies reporting the highest success rates included patients with early postoperative infections(6,8,15–17). In addition, the criteria used to define SAT success or failure also vary across studies. In the only controlled study published to date(18), Siqueira *et al* found a SAT efficacy of 68.5% at five years versus an efficacy of 41.1% in a control group of patients who did not receive SAT selected by a propensity score. The study included patients in whom a potentially curative surgery had been performed, and it considered death as a failure.

The efficacy shown in our study appears acceptable in the context of the population managed by SAT, and this information is useful in decision-making in daily clinical practice. Moreover, our data show (Figure S1) that patients for whom SAT is successful exhibit better symptomatic and functional control than those who experience SAT failure. However, taking into account the implications of maintaining long-term antibiotic treatment, the indication for SAT must be weighed carefully, and the temptation to use this strategy to circumvent the challenge of complex surgeries that can be curative should be avoided(19).

In our study, aetiologies other than gram-positive cocci or localization of the implant in an upper limb were independently associated with SAT failure. The finding that age younger than 70 years is a factor associated with failure is not easily explained, but it may be associated with confounding variables that are related to the frequency of more complex cases in young patients and/or to, the presence of bone tumours, which in a previous study was associated with worse results (20). Therefore, it is likely that anatomical, biological, or microbiological factors that cannot be captured by reviewing the clinical data underlie many SAT failures. Interestingly, few failures were due to the development of antibiotic resistance. It is also relevant that in some cases, failure could be due to the existence of unsuspected microorganisms that were not detected in cultures prior to the initiation of SAT.

Tetracyclines and cotrimoxazole were the most commonly used antibiotics, and their association with adverse effects was low. Few patients had to suspend treatment due to adverse

effects, and in cases in which it was suspended, an alternative regimen could nearly always be offered. The lack of association of success with the class of antibiotic used suggests that priority should be given to safety and tolerability when choosing an antibiotic from those that show microbiological activity against the causative organism.

Our study has obvious limitations. The retrospective nature of the study makes it difficult to obtain detailed information on adverse effects or adherence. In addition, patients with very early failure of SAT were not included, resulting in overestimation of the success rate. The multicentre nature of the study also makes it likely that there was heterogeneity in the choice of antibiotic treatment and surgical management. The failure rate among the centres, as measured by the MOR, was 1.5; this indicates that the risk of SAT failure increases, on average, by 50% according to the centre in which it is performed and suggest that there are differences in the selection or management of patients in different centres (21,22). Despite the fact that a large recruitment period was selected, the mean follow-up time was lower than expected. Only 43 of the successful patients (approximately one quarter of them) were followed for more than 5 years (Figure S2). Finally, the absence of a control group makes it impossible to accurately quantify the benefit of SAT.

However, some of the characteristics of our study demonstrate its value compared to previously published investigations. Our study is the largest published study to date to address the use of SAT for PJIs. Only patients with active infections and whose cure probability was null or extraordinarily low were included. We chose pragmatic criteria to define SAT failure. Nevertheless, the success of SAT may be underestimated because we cannot rule out the possibility that some patients with intermittent fistula benefitted from SAT. Finally, the competing event analysis allowed us to analyse the failure of the patients who were alive at each point examined.

In conclusion, when prescribed by experts who can anticipate the toxicities and interactions that may occur during antibiotic treatment, SAT offers acceptable results in terms of its efficacy and safety for patients for whom surgical treatment is insufficient or is contraindicated due to

disproportionate risks involving the patient's symptoms or his or her life expectancy. Considering the practical (and ethical) difficulties associated with conducting a clinical trial, well-followed prospective cohort studies may continue to advance our knowledge of the complex issue of the use of SAT in PJI.

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Table 1: Characteristics of the patients

	n (302)	%
Sex Male	122	40.4
Age (years) (mean, SD)	75.5±13.9	-
Age >70 years	220	72.8
>85 years	85	28.1
Prosthesis		
Knee	157	52.0
Hip	136	45.0
Upper limb	9	3.0
Number of prostheses placed in the same localization	162	53.6
Primary	108	35.8
Secondary	29	9.6
Tertiary or more		
Classification		
Early postoperative[1]	48	15.9
Late chronic	220	72.8
Haematogenous[1]	34	11.3
Diagnostic criteria		
Fistula	133	44.0
Inflammatory and radiological signs, with elevated CRP and positive culture	107	35.4
Synovial fluid count[2]	73	24.2
Positive culture	280	72.8
Characteristics of the prostheses		
Cemented	106	64.6[3]
Loose	51	23.2[3]
Comorbidity		
Charlson index (median, IQR)	4 (3-6)	-
Diabetes	68	22.5
Solid neoplasm	37	12.3
Congestive heart failure	33	10.9
Kidney failure	31	10.3
Liver failure	18	6.0
Initial clinical symptoms		
Asymptomatic	38	12.6
Pain	180	59.6
Impaired walking	167	55.3
Fistula	133	44.0
Local inflammation	127	42.1
Joint effusion	56	18.5
C-reactive protein (mg/l) (mean, SD)	51.7±63.3	-
Management		
Debridement with partial removal	24	7.9
Debridement without removal	143	47.4
Non-surgical	132	43.7
Reason for non-curative surgical management		
Decision of the surgeon	82	27.2
High surgical risk	80	26.5
Advanced age	71	23.5
Patient´s decision	70	23.2
Anticipation of poor functional results	69	22.8
Presence of minor symptoms	35	11.6

Percentages were calculated relative to the total number of patients. The mean and standard deviation were calculated for normally distributed variables, and the median and interquartile range were calculated for variables with an abnormal distribution. n: number of patients; IQR: interquartile range; SD: standard deviation.

[1]after failure of DAIR.

[2]Only one patient had a synovial count of leukocytes as a unique criterion of PJI.

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Table 2. Aetiology of prosthetic joint infections

Microorganism	n (%)
CoNS	98 (32.5)
S. aureus	94 (31.1)
MSSA	73 (24.1)
MRSA	21 (7.0)
Streptococcus sp.	28 (9.3)
Enterococcus sp.	17 (5.6)
Enterobacteriaceae	26 (8.6)
Escherichia coli	8 (2.6)
Proteus sp.	6 (2.0)
Klebsiella sp.	5 (1.7)
Morganella sp.	3 (1.0)
Enterobacter sp.	2 (0.7)
Citrobacter sp.	1 (0.3)
Non-fermenting GNB	20 (6.6)
Pseudomonas sp.	19 (6.3)
Acinetobacter sp.	1 (0.3)
GPB	10 (3.3)
Cutibacterium sp.	8 (2.6)
Clostridium sp.	2 (0.6)
Fungi	6 (2.0)
Negative culture	22 (7.3)
Polymicrobial	41 (13.6)
High virulence	144 (47.7)

CoNS: Coagulase-negative staphylococci; MSSA: methicillin-sensitive *Staphylococcus aureus*; MRSA: methicillin-resistant *S. aureus*; sp.: species; GNB: gram-negative bacilli; GPB: gram-positive bacilli. "High virulence" is defined as infections caused by *S. aureus*, GNB, and yeast.

Table 2. Aetiology of prosthetic joint infections

Microorganism	n (%)
CoNS	98 (32.5)
S. aureus	94 (31.1)
MSSA	73 (24.1)
MRSA	21 (7.0)
Streptococcus sp.	28 (9.3)
Enterococcus sp.	17 (5.6)
Enterobacteriaceae	26 (8.6)
Escherichia coli	8 (2.6)
Proteus sp.	6 (2.0)
Klebsiella sp.	5 (1.7)
Morganella sp.	3 (1.0)
Enterobacter sp.	2 (0.7)
Citrobacter sp.	1 (0.3)
Non-fermenting GNB	20 (6.6)
Pseudomonas sp.	19 (6.3)
Acinetobacter sp.	1 (0.3)
GPB	10 (3.3)
Cutibacterium sp.	8 (2.6)
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Table 3: Analysis of the variables associated with SAT failure

	Success		Failure		Univariate analysis[1]			Multivariate analysis[2]		
	n	%	n	%	SHR	95% CI	p	SHR	95% CI	p
Sex Male	71	58.2	51	41.8	1.04	0.73-1.48	0.83			
Female	106	58.9	74	41.1	0.99	0.98-1.00	0.08			
Age (years) (mean; SD)	76.3	13.9	74.3	13.9						
Age >70 years	137	62.3	83	37.7	0.63	0.43-0.92	0.02	0.63	0.44-0.91	0.013
Prosthesis										
Knee	94	59.9	63	40.1	0.96	0.68-1.37	0.82			
Hip	81	59.6	55	40.4	0.91	0.64-1.3	0.60			
Upper limb	2	22.2	7	77.8	2.44	1.45-3.97	0.001	2.44	1.91-3.12	0.000
Number of prostheses										
Primary	103	63.6	59	36.4	0.78	0.54-1.11	0.16			
Secondary	56	51.9	52	48.1	1.30	0.91-1.85	0.15			
Tertiary or more	17	58.6	12	41.4	1.02	0.59-1.75	1.00			
Classification										
Early postoperative	25	52.1	23	47.9	1.10	0.7-1.72	0.69			
Late chronic	131	59.5	89	40.5	0.98	0.66-1.45	0.93			
Haematogenous	21	61.8	13	38.2	0.91	0.5-1.65	0.77			
Patient characteristics										
Charlson index (median; IQR)	4	(3-6)	4	(3-6)	0.93	0.86-1.01	0.07			
Fistula	71	53.4	62	46.6	1.10	0.78-1.57	0.58			
Microorganism										
GPC[3]	137	62.6	82	37.4	0.66	0.45-0.96	0.03	0.62	0.41-0.94	0.025
CoNS	62	63.3	36	36.7	0.80	0.55-1.17	0.26			
S. aureus	57	60.6	37	39.4	0.89	0.60-1.32	0.57			
MRSA	8	38.1	13	61.9	1.74	0.94-3.22	0.08			
Enterobacteria	13	50.0	13	50.0	1.40	0.83-2.37	0.21			
Negative culture	7	31.8	15	68.2	1.87	1.09-3.20	0.02			
Polymicrobial	23	56.1	18	43.9	0.99	0.63-1.54	0.96			
Management										
Debridement with partial removal	13	54.2	11	45.8	1.55	0.82-2.90	0.18			
Debridement without removal	87	60.8	56	39.2	0.81	0.57-1.16	0.24			
Non-surgical	76	57.6	56	42.4	1.06	0.74-1.50	0.31			
Antibiotic regime										
Intravenous antibiotics	58	56.3	45	43.7	1.21	0.85-1.73	0.30			
Monotherapy	125	61.6	78	38.4	0.75	0.53-1.07	0.12			
Combined with rifampicin	39	55.7	31	44.3	1.17	0.79-1.73	0.44			
Adverse effects	47	58.0	34	42.0	0.90	0.60-1.35	0.60			

[1]Univariate analysis of the analysed variables and their association with failure of the SAT.

[2]Multivariable model of the variables associated with failure of the SAT.

[3]The analysis included all the GPC (*Streptococci*, *Staphylococci* and *Enterococci)*.

n: number of patients; SD: standard deviation, IQR: interquartile range; SHR: sub-hazard ratio; CI: confidence interval; GPC: gram-positive cocci; CoNS: coagulase-negative staphylococci; MRSA: methicillin-resistant *S. aureus*.

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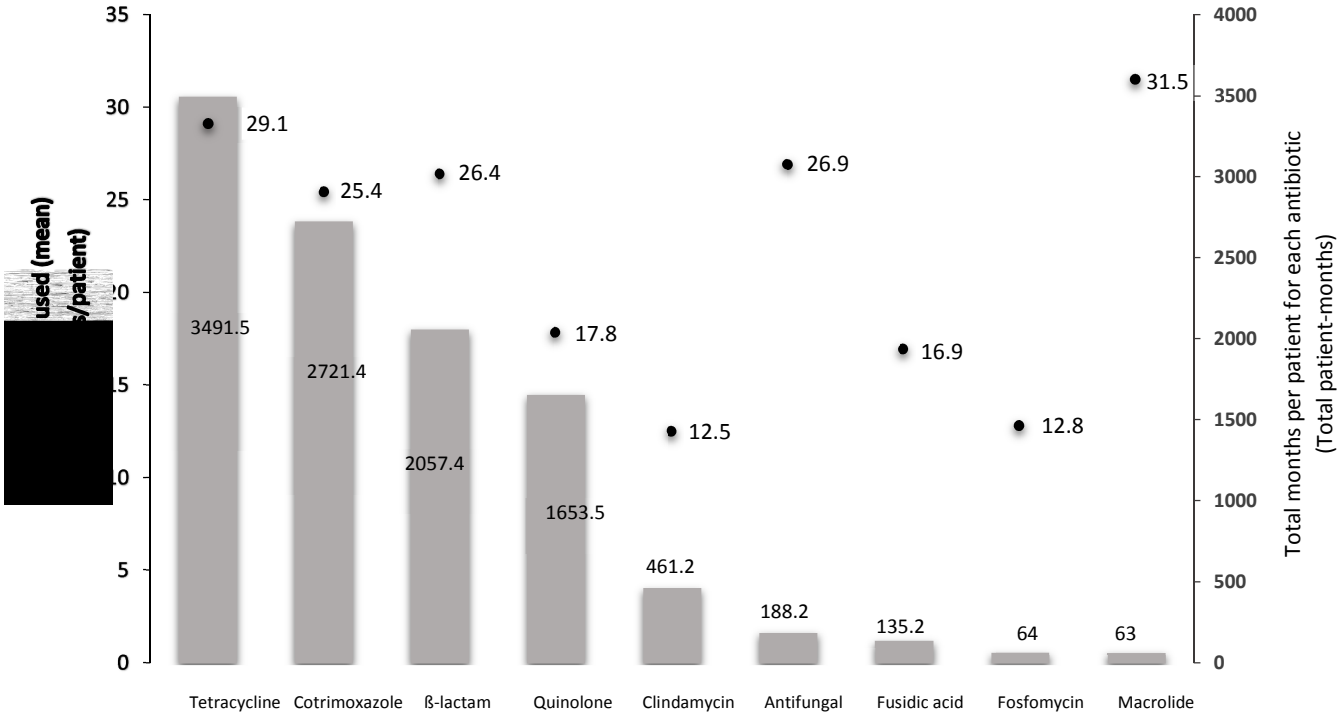
Figure 1: Frequency of antibiotic use



The columns of the graph represent the total number of months of treatment per patient for each type of antibiotic (right axis). The points represent the average duration of use of each antibiotic (left axis).

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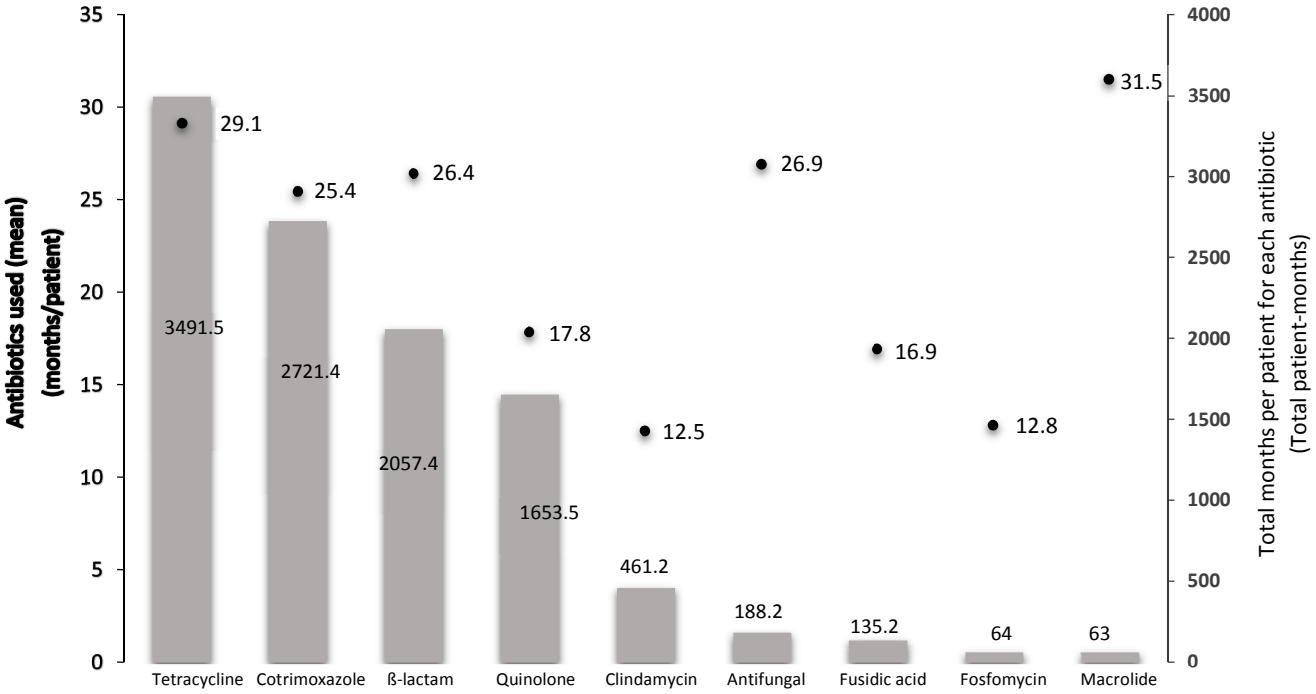
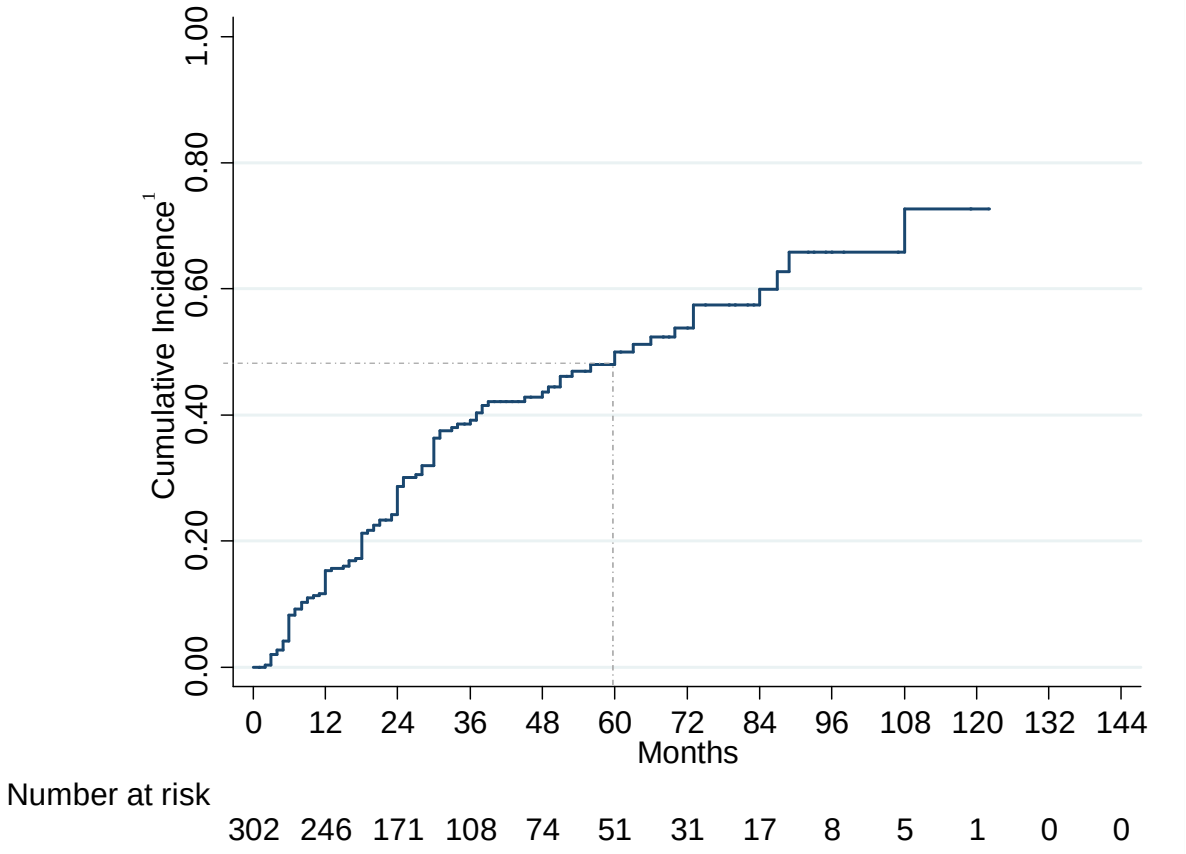


The columns of the graph represent the total number of months of treatment per patient for each type of antibiotic (right axis). The points represent the average duration of use of each antibiotic (left axis).

Figure 2: Estimation of failures: competing-risks regression



[1]Cumulative incidence of exhibiting SAT failure over time.