http://www.jrdiabet.ro
Rom J Diabetes Nutr Metab Dis. **21**(1):55-62
doi: 10.2478/rjdnmd-2014-0009

ANTIMICROBIAL THERAPY IN INFECTIOUS COMPLICATIONS OF DIABETIC FOOT

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received: February 10, 2014 *accepted*: March 01, 2014
available online: March 15, 2014

Abstract

Background and aims: *The treatment of diabetic foot complications is combined, surgical and medical. The aim of our study was to assess the results of antimicrobial therapy in diabetic foot infections.* ***Material and methods:*** *100 patients with diabetic foot infections admitted in the Surgery Clinic "I. Juvara" between December 2010 and February 2011 were analyzed.* ***Results:*** *Mean age at presentation was 58.4±9.74 years for women and 63.2±10.53 years for men. Mean diabetes duration was 12.3 years in men and 15.7 years in women. Patients with peripheral arterial disease represented 45% of cases, patients with neuropathy represented 16% of cases and patients with both conditions 39% of the cases. 41 patients suffered minor surgical interventions, 36 patients experienced minor amputations and 23 major amputations (below or above the knee). Antibiotic treatment included cephalosporins, fluoroquinolones and combinations with Metronidazole. After treatment, 74% of patients had a good postoperative evolution. For 26 patients a change of the antibiotic was necessary but only in 10 cases this was made according to antibiogram.* ***Conclusions:*** *Surgical debridement and wound management, carefully chosen antimicrobial therapy and treatment of comorbidities are very important for a successful outcome. Initial empirical antibiotic selection should be followed by culture-guided definitive therapy.*

key words: *diabetic foot, antimicrobial therapy, amputations*

Background and aims

Diabetes is a disease with multiple implications for individuals, but also for society. In Romania, the prevalence of diabetes is currently estimated at 8% of the population [1]. Within 10-15 years from disease onset, 25% of type 2 diabetic patients develop ischemic/neuropathic lesions of the lower limb included in the term "diabetic foot". It defines the lesions that diabetes causes to the nerves, bones and soft tissues [2].

The annual incidence of diabetic foot is 2% of people with diabetes and its prevalence is 25% of diabetic patients [3]. Limb pathology represents 55% of total diabetic surgical problems. 14-24% of patients with diabetic foot require at some point amputation. These patients are usually hospitalized for 30-40 days/year.

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Some of them (approximately 18%) will be eventually medically retired following amputation [4].

The surgical treatment of diabetic foot infections consists of incision, excision, debridement, fasciotomies, minor and major amputations. The medical treatment consists of metabolic control improvement, blood glucose control, neurotrophic vitamins, vasodilatation drugs and antibiotics [5].

In terms of treatment, the novel antibiotics cover a large antimicrobial spectrum; they have a good penetrability and attain high enough concentrations in the tissues [6]. Use of antibiotics combined with the surgical intervention allows in many cases a less extensive surgery [5].

In our department we use a combination of broad-spectrum intravenous antibiotics, able to cover the entire bacterial spectrum, including anaerobic germs. The most effective antibiotics are the third and fourth generation cephalosporins, but in their absence we can use combinations of antibiotics that will include Metronidazole [7]. The intravenous treatment with antibiotics is maintained for a minimum of 5 days, afterwards it can continue orally, according to the antibiogram.

The aim of our study was to investigate patients with diabetic foot infectious complications and to report the results of antimicrobial therapy in an unicentric series of patients.

Material and methods

100 patients of the Surgery Clinic "I. Juvara", "Dr. I Cantacuzino" hospital were analyzed between December 2011 and February 2012. All cases were admitted with diabetic foot infections as complications of different stages of peripheral arterial disease, neuropathy or both. We included in our study all patients admitted in our Surgery ward with diabetic foot lesions in need of treatment.

Statistical analysis

This was a retrospective observational study. Qualitative variables were expressed as percentages, and quantitative variables were expressed as means ± SD (standard deviation). For continous variables an unpaired Student's t-test was used to compare the mean age in female and male patients. The χ^2 test for categorical predictor variables or Fisher's exact test was used to test for gender and age differences in the incidence of diabetic foot infections, number of amputations, comorbidities and outcome of therapy. P-value was calculated and statistical significance was defined for $p<0.05$.

Results

Study population

The study group included 100 patients. Distribution by gender was: female 28 patients (28%) / male 72 patients (72%). Thus, overall we noticed a higher incidence of diabetic foot complications in men compared to women ($p=0.047$). From the 100 patients, 94 had type 2 diabetes mellitus (DM) and 6 had type 1 DM. Other demographic and social characteristics of the study group are given in Table 1, divided by sex and type of DM.

From 94 cases with type 2 DM, only in 60 we could obtain a definite date for the onset of disease. From these, 48.33% (n=29) belonged to the group with 10-20 years of diabetes evolution. Overall, most patients (n=63) belonged to the 50 - 70 years old age group (Figure 1). Because 5 patients were transferred from another department, we analyzed the blood glucose at admission only in 95 patients. In this group, 52.63% (n=50) of patients showed blood glucose values at admission higher than 200 mg/dl, with a maximum value of 540mg/dL, suggestive for

uncontrolled diabetes. Glycosylated hemoglobin should be a better indicator, but was not available for all patients.

Table 1. Demographic and social characteristics of the study group.

Sex	Males		Females	
Type of DM	Type 1 DM	Type 2 DM	Type 1 DM	Type 2 DM
No.	4	68	2	26
Mean age (years)	52	62,8	49	58,3
Mean evolution of DM (years)	10	12.3	10.5	15.7
Urban/ rural	3/1	48/20	2/0	12/14
Smoking	2	33	1	6

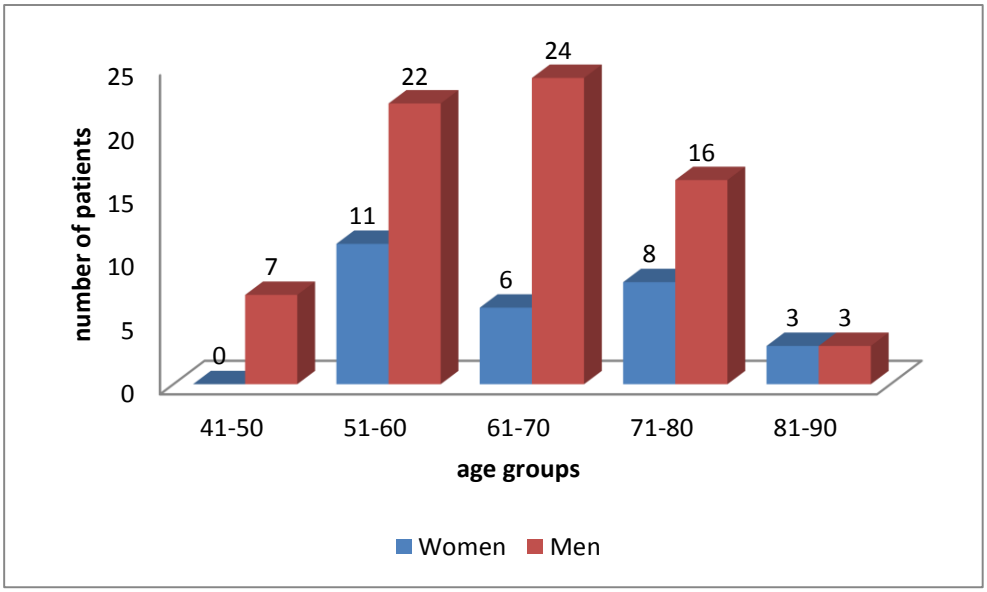

Figure 1. *Distribution of patients in age groups according to sex.*

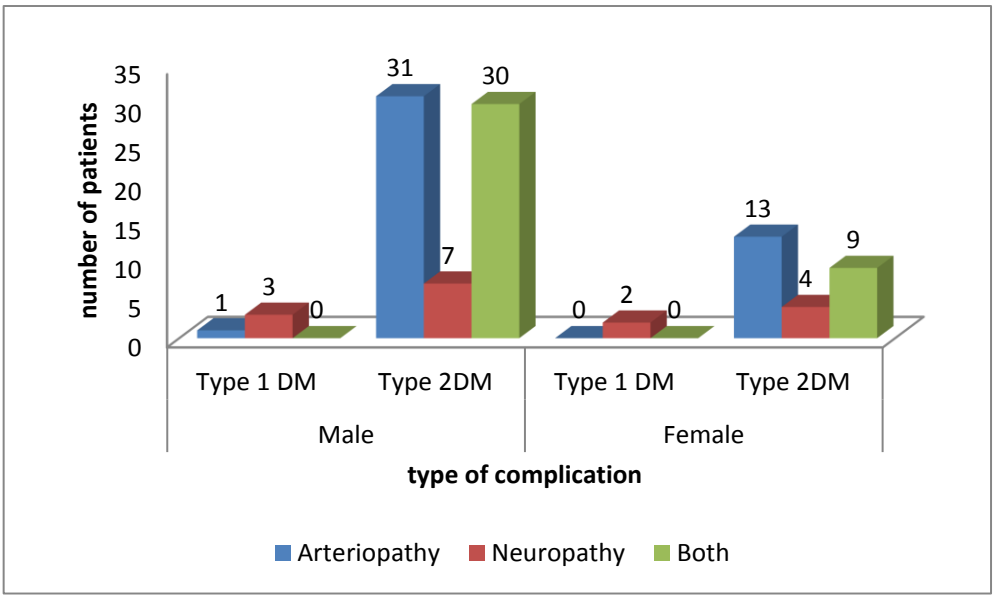

Figure 2. *Frequency of arteriopathy/neuropathy according to sex and type of diabetes.*

For the studied group, 47% of patients were treated only with insulin, 39% were treated with oral antidiabetics alone while 14% used combined insulin and oral treatment.

Patients with peripheral artery disease alone represented 45% of cases, patients with diabetic neuropathy alone represented 16% of cases and patients with both pathologies represented 39% of cases as shown in Figure 2.

Hypertension was observed in 58% cases, ischemic heart disease in 28%, myocardial infarction in 5%, congestive heart failure in 11%. 13% of patients had a history of stroke and 25% had chronic kidney disease (CKD).

In our study group, 49% of patients did not have previous surgery for diabetic foot until admission, 34% had undergone surgery once for diabetic foot complications, 11% had 2 or 3 interventions and 6% had multiple foot interventions. We found a higher frequency of previous surgery in men compared to women (p=0.038) with type 2 DM patients, as shown in Figures 3 and 4. The low number of cases with type 1 DM did not allow for statistical evaluation.

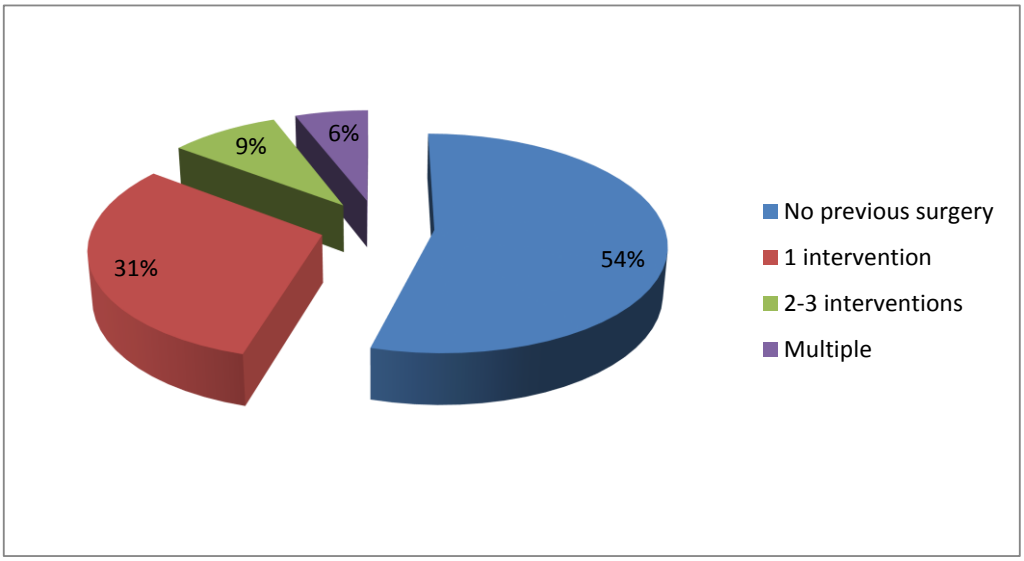

Figure 3. *Frequency of previous foot surgery in males with Type 2 DM.*

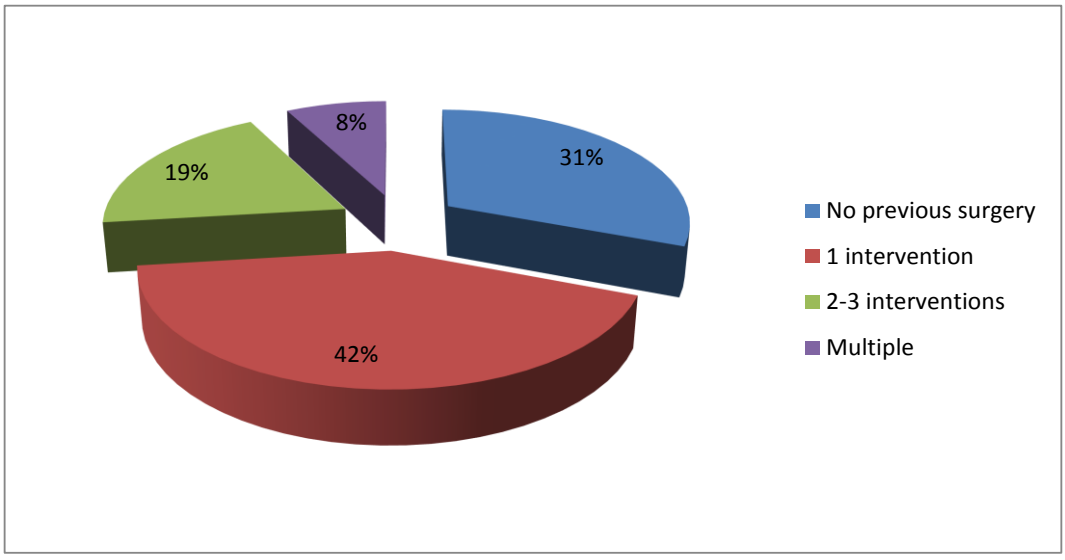

Figure 4. *Frequency of previous foot surgery in females with Type 2 DM.*

41% of the patients received minor surgical interventions like incision, excision, debridement and fasciectomy. 36% of patients experienced minor amputations while 23% major amputations (below or above the knee). From the 59 amputations performed, 32.20% (19 interventions) were performed in arteriopathy alone patients and 52.54% (31 interventions) in patients with both arteriopathy and neuropathy. Patients with neuropathy alone represented 15.25% of amputations (9 interventions) as shown in Figure 5.

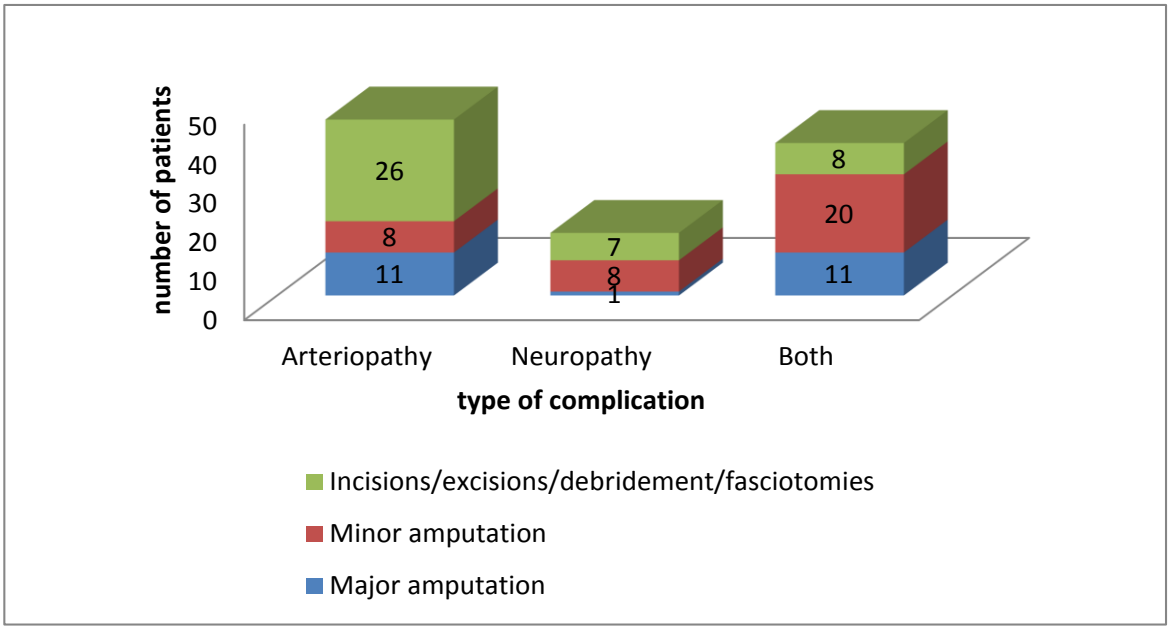

Figure 5. *Type of surgery according to the pathogenic cause of diabetic foot.*

Comorbidities and patient prognosis

Comorbidities influence the patient prognosis operated for diabetic foot pathology, most frequent cardiovascular diseases, followed by lower limb peripheral arterial disease, acute and chronic renal failure, sepsis and anemia. Risk for foot ulcer was significantly increased in patients with cardiovascular disease (OR=2.75 95% CI 1.67-3.21), lower limb peripheral arterial disease (OR=4.96 95% CI 1.55-6), chronic kidney disease (CKD) (OR=1.49 95% CI 0.97-4.90). Acute renal failure (ARF) is an aggravating factor, 10% of patients requiring supportive treatment in this regard. ARF was developed due to sepsis, fluid volume imbalances or altered pump function of the heart. CKD is associated with an increased risk of amputation, this being the case in 10% of patients in our study.

Antibiotic treatment used in the study group

All patients included in the study received antibiotic treatment during the current hospitalization. This was initially empirically chosen but it was subsequently changed according to the antibiogram if local evolution was not favorable. 13 patients (13%) received combined antibiotic treatment while 87 patients (87%) received initial antibiotic monotherapy. The most used antibiotics were cephalosporins (CFS), like Cefazolin, Cephalexin (CFS I), Cefuroxime (CFS II), Cefoperazone/Sulbactam, Ceftriaxone, Cefpirome, Ceftazidime (CFS III). We also used fluoroquinolones (Ciprofloxacin and Norfloxacin), Clindamycin and Metronidazole (for anaerobic germs). The proportion of patients receiving different antibiotic regimens is shown in Table 2.

Table 2. Proportion of patients receiving different antibiotic regimens.

	Number of patients
CFS I	2
CFS II	7
CFS III	68
Fluoroquinolones	7
Metronidazole	3
Combinations	
Cefazolin + Metronidazole	2
Cefuroxime + Metronidazole	1
Cefoperazone / Sulbactam + Metronidazole	3
Ceftriaxone + Metronidazole	3
Ceftazidime + Metronidazole	2
Ciprofloxacin + Clindamycin	1
Cefoperazone / Sulbactam+Clindamycin	1

After antibiotic treatment, 74% of patients had a good postoperative evolution, 9% of patients a slow favorably evolution and 17% of patients an initial unfavorable evolution. Thus, for these 26 patients, either a change of the antibiotic, surgical re-intervention or both were necessary.

In 26 cases (26%), a change of the antibiotic regimen was necessary, in 16 patients (16%) due to the local unfavorable evolution and in 10 patients (10%) following the culture/antibiogram result. This identified *Staphylococcus aureus* in 5 cases, *Escherichia coli* in 2 cases and one case each of *Enterobacter spp.*, *Enterococcus* and *Alcaligenes faecalis*.

Antibiotics initiated according to the antibiogram result included aminopenicilins (Amoxicillin/Clavulanic acid, Ampicillin), carbapenems (Meropenem), sulfonamides (Sulfamethoxazole) and polypeptides as shown in Table 3.

For Imipenem, we detected antibiotic resistance in one case and an intermediate result was obtained in another test as shown in Table 4.

Table 3. Antibiotics initiated according to antibiogram result.

Antibiotic	Number of patients
Ciprofloxacin	3
Norfloxacin	1
Ceftriaxone	1
Amoxicillin / Clavulanic acid	1
Ampicilin	2
Sulfamethoxazole	2
Meropenem	1
Colistin	1

Discussions

Diabetic patients have a 15-fold higher risk of amputation, but half of these amputations can be prevented if patients are treated early and have a good glycemic control [8]. The major cause of amputation in DM is the development of a foot ulcer. In our study, peripheral arterial disease was the most frequent cause (45% of cases) and almost half of the patients had previous surgery related to diabetic foot complications prior to admission. Overall we performed 59 amputations, of which 23 major ones. All patients received antibiotic treatment, especially cephalosporins.

Diabetic foot ulcerations usually occur during the fifth to seventh decade of life [9]. Similar to other studies [10,11], 86% of patients in our study were older than 50 years.

Hamalainen et al. [12] mentioned a higher rate of amputations among males, but some studies did not confirm this finding [13]. In our study, the male-to-female ratio was 2.57, highlighting the male predominance. The higher incidence of diabetic foot complications in men could be caused by a more demanding physical activity, higher frequency of smoking and lower compliance to medical treatment, resulting in a higher incidence and severity of the peripheral artery disease in men [14]. In addition to age over 50 years, male gender, rural area, poor socio-economic status and poor glycemic

control, the medical literature mentions smoking as a risk factor [15]. Comorbidities, like cardiovascular disease, lower limb peripheral arterial disease, presence of anemia, sepsis, ARF or CKD influence the patient prognosis with diabetic foot pathology.

Table 4. Results of antibiogram testing for different antibiotics used in the study patients.

Tested antibiotic	No. of tests	Susceptible	Intermediate	Resistant
Amikacin	4	2	-	2
Ampicillin	8	5	-	3
Amoxicillin / Clavulanic acid	6	3	-	3
Azythromycin	4	1	1	2
Cefoperazone	8	3	2	3
Cefoxitin	2	2	-	-
Ceftazidime	5	3	-	2
Ceftibuten	1	-	-	1
Ceftriaxone	8	4	-	4
Cefuroxime	9	5	1	3
Ciprofloxacin	9	5	-	4
Clindamycin	3	3	-	-
Cotrimoxazole	11	8	-	3
Colistin	1	1	-	-
Doxycycline	1	-	-	1
Gentamicin	11	8	-	3
Imipenem	6	4	1	1
Linezolid	1	1	-	-
Meropenem	2	2	-	-
Netilmicin	4	3	-	1
Norfloxacin	10	6	-	4
Ofloxacin	1	-	-	1
Oxacilin	6	5	-	1
Penicillin	6	2	-	4
Rifampicin	3	2	-	1
Teicoplanin	1	1	-	-
Tobramycin	4	3	-	1
Vancomycin	6	6	-	-

Previous surgical interventions lead to a high degree of tissue altering, increasing the risk of developing a new lesion by changing the foot statics, frequently with polymicrobial lesions and a possible polychemoresistance of the existing bacteria [16].

The most widely used antibiotics in our Surgery Department were CFS III (Ceftriaxone, Cefoperazone/sulbactam, Ceftazidime), CFS II (Cefuroxime) and fluoroquinolones (Ciprofloxacin, Norfloxacin), and in their absence we can use combinations of antibiotics that will not lack Metronidazole.

Ampicillin, Biseptol, Colistin and Meropenem were chosen as an alternative for the polychemoresistance cases. Antibiotics commonly used for the treatment of diabetic foot for which resistance was detected in a higher percentage were represented by Ceftriaxone, Ciprofloxacin and Norfloxacin.

Conclusions

In our study cephalosporins were the most used antibiotics, followed by fluoroquinolones. When performing pathogen susceptibility tests, the antibiotics commonly used to treat diabetic foot infections for which the germs have developed resistance were Ceftriaxone, Ciprofloxacin and Norfloxacin. As a second choice antibiotic, Imipenem showed resistance in

just one case and an intermediate result in another one. Useful alternatives for the polychemoresitance cases were penicilines, carbapenems, sulfonamides and polypeptides.

The current therapeutic attitude in diabetic foot complications is the use of antibiotics combined with surgery. It is important to isolate the specific pathogen especially in extended limb infections and for situations that are likely to require prolonged therapy. Definitive therapy based on antibiogram would reduce the number of antibiotics, narrow the spectrum and avoid bacterium resistance.

Nevertheless, presence of distal lesions associated with peripheral arterial disease represented an important risk factor for a major amputation, regardless of the antibiotherapy that was used.

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