

How Much Resistance is Considered During Prophylaxis Recommendation? A Case Report of Infective Endocarditis with Multi-Drug Resistant *Streptococcus* Despite Appropriate Prophylaxis Before Dental Intervention

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ABSTRACT Infective endocarditis is a disease with high mortality and morbidity, generally caused by a wide range of organisms. Prophylaxis with penicillins, cephalosporins, macrolides, or vancomycin is highly recommended for the patients with endocarditis, prosthetic heart valves. An 83-year-old man admitted with fever, fatigue, and joint pain and reported dental intervention following amoxicillin prophylaxis forty-five days ago. Patient history indicated acute rheumatoid arthritis, bacterial endocarditis, and mitral and aortic valve replacement. *S. sanguinis* was detected in the blood culture of the patient, which was resistant to penicillin and ampicillin. He was given meropenem, the clinical status was improved and no microorganisms were detected in two follow-up blood cultures. Endocarditis prophylaxis should be individualized considering the globally high penicillin resistance, especially for the patients with prosthetic valves and/or infective endocarditis history. In addition, to decrease the bacterial load of the oral flora before elective dental or respiratory intervention is recommended with antibiotic prophylaxis.

Keywords: Infective endocarditis; antibiotic prophylaxis; antibiotic resistance; *S. sanguinis*

Infective endocarditis is an infectious disease with high mortality and morbidity. The most common microorganisms causing infective endocarditis are *S. aureus*, *S. viridans*, *S. gallolyticus*, HACEK group microorganisms (*Haemophilus spp*, *Aggregatibacter spp*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella spp*), and community-acquired enterococci. The prophylaxis of infective endocarditis before dental and respiratory interventions can be done for those patients that can have oral tablets by amoxicillin and for those who cannot, by ampicillin, cefazolin, or ceftriaxone. For those patients who are allergic to penicillins, clindamycin, azithromycin, clarithromycin or vancomycin can be suggested.¹⁻⁵

Streptococcus sanguinis is a facultative anaerobic bacterium that can be found in normal oral flora and is one of the most common bacteria of viridans streptococci group. When the microorganisms of this group are evaluated for antibiotic susceptibility, it has been shown that they are susceptible to penicillin (59.8%), ampicillin (62%), erythromycin (63.5%), clindamycin (83.8%), ceftriaxone (91.6%), cefotaxime (92.3%), levofloxacin (97.1%) and vancomycin.³ Penicillins are still the first choice for prophylaxis and amoxicillin is recommended by guidelines, and in case of penicillin allergy first choice is clindamycin.^{2,4-6}

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In this case report, we present a case of infective endocarditis developed in a patient with valve prosthesis following a dental intervention despite appropriate antibiotic prophylaxis and evaluate the antibiotics used in prophylaxis regarding the resistance in microorganisms.

CASE REPORT

A male patient aged 83 years admitted to the hospital with fever, joint pain, and fatigue. The patient stated that the fever was going on for the last month and occasionally was measured as 38°C, accompanied by chills and he simultaneously experienced urinary tract pain and a decrease in the amount and frequency of urination. Based on these signs and symptoms, the patient had been diagnosed as prostatitis and treated empirically with ciprofloxacin for 20 days, however, his complaints were not ceased with this treatment. The patient also added that he had a dental intervention 1.5 months ago and received amoxicillin for endocarditis prophylaxis.

His medical history includes mitral and aortic valve disorder secondary to acute rheumatism and had bacterial endocarditis 26 years ago. He had mitral and aortic valve replacement 17 years ago. At the time of admission to our clinics, the patient was being followed up for heart failure, tricuspid valve failure, hypertension, and benign prostate hypertrophy and treated with carvedilol, spironolactone, dutasteride, and warfarin.

The physical examination revealed dysrhythmia, a systolic murmur of grade 1-2/6, inspiratory rales that are most prominent at lower lobes. The abdominal examination was normal. Varicose enlargements were observed at lower extremities and scar tissue of previous surgery was observed in the thoracic region. Oral hygiene of the patient was unremarkable, without any problems. No gingivitis or tooth decay was observed. The patient stated that he didn't use any toothpicks or dental floss.

The abnormal laboratory values of the patient were as follows (normal ranges are provided in parenthesis): serum creatinine 2.11 mg/dl (0.8-1.3), blood urea nitrogen 47.0 mg/dL (8-23), alkaline phosphatase 186 U/L (25-100) C-reactive protein: 5.12

mg/dl (0-0.5), rheumatoid factor 27 IU/ml, erythrocyte sedimentation rate 35 mm/hour (0-24). The microscopic evaluation of the urine did not reveal any significant finding except for 1-2 leucocytes and no bacteria were seen in urine culture.

Blood samples were collected in two consecutive days and cultured for microbial reproduction. A positive alarm was observed 24 hours after the first culture and 28 hours after the second culture and gram staining revealed positive cocci. Bacteria were identified with MALDITOF MS (BRUKER, Microflex) (Bremen, Germany). The reproduced bacteria in the culture were identified as *S. sanguinis*. Antibiotic susceptibility was tested by Gradient Strip and the results were evaluated according to EUCAST 2018 standards. The minimum inhibitory concentrations were 3 mg/L for benzylpenicillin (resistant), 16 mg/L (resistant) for ampicillin, 1 mg/L (resistant) for ceftriaxone, 1 mg/L (susceptible) for vancomycin, 0.50 mg/L for teicoplanin (susceptible), and 0.50 mg/L for meropenem (susceptible).

The echocardiographic evaluation showed that the left atrium was dilated, left ventricle wall thickness was normal, and their inner diameters were increased. Ejection fraction was 35% and cardiac muscle was generally hypokinetic and septum was moving paradoxically. Bioprosthetic walls were visible and degeneration was observed on mitral valve and mitral and tricuspid valve insufficiency was observed. There was no vegetation. Transesophageal echocardiographic (TEE) evaluation revealed no vegetation.

As the patient had prosthetic valves, previous history of bacterial endocarditis (it developed 26 years ago and the causative agent is unknown), and no other infection site was found, he was hospitalized and empirical vancomycin treatment was initiated with the prediagnosis of infective endocarditis. *S. sanguinis* was isolated from the blood cultures and reevaluated by infectious diseases clinics. As the patient had two positive blood cultures, high fever, predisposing cardiac disease, and positive rheumatoid factor, infective endocarditis diagnose was made as one major and three minor criteria were present suggested by Modified Duke Criteria.⁷ As *S. sanguinis* was resistant to penicillin and ceftriaxone and the patient had renal failure, vancomycin was stopped due

to its nephrotoxicity and meropenem treatment was initiated following dose adjustment according to the patient's glomerular filtration rate. Blood culture was repeated one week after the initiation of the treatment and no bacterial growth was observed. Treatment was continued for 6 weeks.

After treatment, echocardiographic evaluation showed that ejection fraction of the patient increased from 35% to 48% and no vegetation was observed as in the first echocardiogram.

The patient was informed about the procedures and the possible use of his data for scientific purposes and his consent was received.

DISCUSSION

The patients with a previous history of infective endocarditis and with prosthetic valves are considered as the highest risk population for infective endocarditis, diagnosis of which is made according to Modified Duke Criteria.⁷ In this case, the major criterion was positive blood culture and fever, predisposing cardiac disease, and positive rheumatoid factor were three minor criteria based on which the diagnosis of infective endocarditis was made. Although positive echocardiographic findings were also one of the major criteria, the transthoracic (TTE) and transesophageal (TEE) echocardiographic evaluation of the patient had not revealed any vegetations. While the sensitivity of TTE in showing the prosthetic valve vegetations is about 50%, TEE's sensitivity increases to 92% in this regard and its specificity is 90%. However, in cases with previous valvular lesions (mitral valve prolapses, degenerated calcified lesions, etc.) and if the vegetation is smaller than 2-3 mm. it is difficult to observe them.⁷

In this case infective endocarditis was developed following a dental intervention performed 5-6 weeks ago, despite prophylactic amoxicillin. The patient's oral hygiene was not problematic and he had no other risk factors except the prosthetic valve, previous history of infective endocarditis, and tooth extraction. *S. sanguinis* was isolated from two consecutive blood cultures and the antibiotic susceptibility test showed that the bacteria was resistant to penicillin, ampicillin, and cephalosporin. Thus, we were facing a case of in-

fective endocarditis developed despite the antibiotic prophylaxis in accordance with the current guidelines. The blood culture was performed as the patient's fever was not dropped despite the 20-day administration of ciprofloxacin for prostatitis and it was positive for *S. sanguis*. According to Eucast 2018, there are no threshold values for ciprofloxacin resistance. Development of endocarditis despite the usage of quinolone antibiotics suggested they may not be effective for the prophylaxis of endocarditis. According to guidelines, a fluoroquinolone (ciprofloxacin, levofloxacin, or moxifloxacin) may be considered as an alternative agent for the patients unable to tolerate ceftriaxone (or other third- or fourth-generation cephalosporins).⁵ Ciprofloxacin was used for the treatment and prophylaxis of endocarditis, mainly because of its oral use advantage and it was shown to be effective although the development of resistance was reported.⁸

According to a study performed in Turkey, *S. sanguinis* was consisting of 16.3% of the viridans group streptococci isolated from infective endocarditis patients and 75% was resistant to penicillin and ampicillin.⁹ In another study conducted on various patient groups including mainly hematologic malignancy cases, more than 50% resistance was observed among viridans group streptococci.^{10,11}

Several international guidelines generally suggest a similar approach. Following recommendations of 2008 National Institute of Health and Care Excellence (NICE) guidelines prophylactic antibiotic usage decreased by more than 75%. However, due to a significant increase in infective endocarditis incidence during the following years, the guideline changed the phrase "routine prophylaxis is not recommended" to "prophylaxis is recommended for high-risk patients" as suggested by other guidelines.¹²

According to a study performed to evaluate the efficacy and the necessity of the antibiotic prophylaxis, 266 patients that will have tooth extraction randomized in 5 groups (control; 1000/200 mg amoxicillin + clavulanic acid; 2 g amoxicillin; 600 mg clindamycin; or 600 mg azithromycin).¹² Blood samples were collected from each patient before antibiotics and 30 seconds, 15 minutes, and 1 hour

after tooth extraction and evaluated for bacteremia. Bacteremia incidence in the blood samples taken 30 seconds after the extraction was 0% only for amoxicillin + clavulanic acid group, 50% for amoxicillin, 87% for clindamycin and 81% for azithromycin groups. On the other hand, the decrease in bacteremia was shown on the blood samples that were taken 15 minutes after the procedure, 18% for the control group, 0% for the amoxicillin + clavulanic acid, 4% for the amoxicillin, 19% for the clindamycin, and 18% for the azithromycin groups. Based on these results, the authors suggested alternative prophylaxis regimens for the patients allergic to β -lactam antibiotics. However, amoxicillin + clavulanic acid was given via intravenous infusion, while the other antibiotics were given orally 1-2 hours before the procedure suggested serious methodologic bias in this study as pharmacokinetic profiles and mechanisms of effects of the antibiotics were probably not taken into consideration while planning this study.¹³

In another study, 160 patients that will have tooth extraction were randomized in 4 groups: control, mouth wash with chlorhexidine, 3 g amoxicillin or 600 mg clindamycin.¹⁴ Bacteremia was detected in 35% of the control group, 40% of the chlorhexidine group, 20% of the clindamycin group and 7.5% of the amoxicillin group.¹⁴

Vegetations may not be detected in cases of very small vegetations, mitral valve prolapses, degenerative lesions and presence of prosthetic valves. Infective endocarditis can be observed with a rate of 15% despite negative echocardiographic findings. Moreover, normal echocardiographic findings do not exclude infective endocarditis diagnosis, even if it is performed transesophagically. Thus, the echocardiographic evaluation must be repeated in 7-10 days.¹⁵

In conclusion, antibiotic prophylaxis is still indispensable, especially for patients with high risk, as the case presented here. However, it is debatable to suggest penicillin group antibiotics for populations with high antibiotic resistance as the first choice for prophylaxis. For patients with infective endocarditis and prosthetic heart valve like this case, it is rational to individualize prophylaxis and plan specifically for that patient. Combining antibiotics with different mechanisms of actions and decreasing oral flora bacterial load via topical oral antiseptic application are the other approaches that may decrease the risk of infective endocarditis.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, shareholding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Müberra Devrim Güner, Semra Tunçbilek; **Design:** Müberra Devrim Güner, Semra Tunçbilek; **Control/Supervision:** Müberra Devrim Güner; **Data Collection and/or Processing:** Emel Bayrak; **Analysis and/or Interpretation:** Müberra Devrim Güner, Emel Bayrak; **Literature Review:** Müberra Devrim Güner; **Writing the Article:** Müberra Devrim Güner, Emel Bayrak; **Critical Review:** Müberra Devrim Güner; **References and Fundings:** Müberra Devrim Güner; **Materials:** Serpil Taşdelen, Emel Bayrak.

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