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GROWTH AND GROWTH TIME EVALUATION OF ISOLATES IN AEROBIC AND ANAEROBIC ADULT BLOOD CULTURE BOTTLES

AEROBİC VE ANAEROBİC YETİŞKİN KAN KÜLTÜRÜ ŞİŞELERİNDE İZOLATLARIN ÜREMESİ VE ÜREME SÜRELERİNİN DEĞERLENDİRİLMESİ

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ABSTRACT

In this study, we aimed to interpret the effect of using aerobic and anaerobic blood culture bottles together and the blood volume taken in the detection of circulatory system infections as soon as possible. Blood cultures were determined using BD BACTEC 9240 (Becton Dickinson, USA) as well as standard microbiological methods. The growth and growth times of isolates in aerobic and anaerobic blood culture bottles were compared and measured. 8178 out of a total of 11234 blood culture bottles were evaluated. Microbial growth was detected in 974 (11.9%) blood cultures. The main pathogens considered causative agents are coagulase-negative staphylococci 114 (18%), *S. aureus* 108 (17.1%), *Klebsiella spp* 86 (13.6%)., *E. coli* 63 (9.9%)., yeast 45 (7.1%)., and *Acinetobacter spp* 43 (6.8%) were detected. The clinically significant growth rate in blood cultures was 6.3%. While the false positive rate was 0.2%, the false-negative rate was 0.06%. In 11% of clinically significant isolates grown in blood culture bottles, growth was observed only in the anaerobic bottle. Most of the growth of *Acinetobacter spp, Pseudomonas sp* and yeast were detected in the aerobic bottle compared to the anaerobic bottle ($P<0.05$). Mean positive signal times were 18.5 and 20.9 hours for aerobic and anaerobic bottles, respectively. It has been concluded that the combined use of aerobic and anaerobic blood culture bottles and the volume of blood drawn are invaluable in the rapid detection of bloodstream infections.

Keywords: Aerobic and Anaerobic, Blood Culture, Coagulase Negative Staphylococci, Reproduction Time, Yeast.

ÖZET

Bu çalışmada dolaşım sistemi enfeksiyonlarının en kısa sürede tespitinde aerobik ve anaerobik kan kültürü şişelerinin birlikte kullanılmasının ve alınan kan hacminin etkisinin yorumlanması amaçlandı. Kan kültürleri, standart mikrobiyolojik yöntemlerin yanı sıra BD BACTEC 9240 (Becton Dickinson, ABD) kullanılarak belirlendi. İzolatların aerobik ve anaerobik kan kültürü şişelerinde büyüme ve büyüme süreleri karşılaştırıldı ve ölçüldü. Toplam 11234 kan kültürü şişesinden 8178'i değerlendirildi. 974 (%11.9) kan kültüründe mikrobiyal üreme saptandı. Etken ajan olarak kabul edilen başlıca patojenler koagülaz negatif stafilokoklar 114 (%18), *S. aureus* 108 (%17,1), *Klebsiella spp* 86 (%13,6), *E. coli* 63 (%9,9), maya 45 (%7,1).) ve *Acinetobacter spp* 43 (%6,8) tespit edildi. Kan kültürlerinde klinik olarak anlamlı büyüme oranı %6.3; yanlış pozitif ve negatif oranları sırasıyla %0.2, %0.06 olarak görüldü. Kan kültürü şişelerinde büyütülen klinik olarak anlamlı izolatların %11'inde sadece anaerobik şişede üreme gözlendi. Kullanılan kan kültürü şişelerinden *Pseudomonas sp, acinetobacter spp* ve mantar üremelerinin büyük kısmı anaerobik şişeye kıyasla aerobik şişede görülmüştür ($P <0.05$). Aerobik ve anaerobik şişelerin ortalama sinyal süreleri sırasıyla 18.5 ve 20.9 saat olarak gözlendi. Tüm bulgular sonucunda Aerobik ve anaerobik kan kültürü şişelerinin birlikte kullanılmasının ve alınan kan hacminin kan dolaşımı enfeksiyonlarının hızlı tespitinde çok değerli olduğu sonucuna varıldı

Anahtar kelimeler: Aerobik ve anaerobik, Kan kültürü, Koagülaz negatif stafilokoklar, Maya, Üreme zamanı.

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INTRODUCTION

Circulatory system infections can be self-limiting or cause serious clinical symptoms such as life-threatening sepsis, multiple organ failure, and disseminated intravascular coagulation (Arabacı & Kutlu, 2019). These infections are one of the main reasons for morbidity and mortality (Mushtaq et al., 2016). Therefore, early diagnosis and appropriate treatment of circulatory system infections are clinically valuable. Blood cultures play a role in determining the microbial etiology and in guiding the treatment in cases of suspected infection. The increase in the older age group in society, the prolongation of the life expectancy of those with chronic diseases, the widespread use of immunosuppressive drugs, and the increase in invasive interventions for diagnosis and treatment are among the factors that increase the incidence of sepsis. Hospital-acquired sepsis is more common in hospitals with high bed capacity, intensive care units, and frequent invasive procedures (Johnstone et al., 2018; Yavuz et al., 2019)

In recent years, in addition to bacterial invasion of the bloodstream, the importance of yeast agents such as *Candida albicans* has been increasing. This microbiological change is probably due to the risk factors that patients have. With the change in the susceptible patient profile, the organisms responsible for bacteremia have also changed. While methicillin-resistant *S.aureus* (MRSA) bacteremia was rare in the 1970s, MRSA is present in more than 40% of patients who develop *S.aureus* bacteremia today (Hassoun et al., 2017; Mayer et al., 2013). Vancomycin-Resistant *Enterococci* (VRE) and Gram-negative bacteria expressing extended-spectrum β-lactamases (ESBL) are also more frequently isolated (Zhou et al., 2017). While the common agents in community-acquired sepsis are *Streptococci, S. aureus*, and *E.coli*, the most common agents in hospital-acquired sepsis are *E. coli, Klebsiella spp, Pseudomonas spp, S. aureus*, and *Enterococci* (Chen & Hsueh, 2012; Haque et al., 2018) Studies on the microbiology of bacteremia show an increased incidence of polymicrobial infections. While almost all bacteremia cases were caused by a single organism in the 1930s, it was reported that approximately 10% of bacteremia cases were caused by more than one organism in the early 1990s (Hall & Lyman, 2006). In addition, the mortality rate in polymicrobial bacteremia is higher than in monomicrobial bacteremia. In most polymicrobial infections, *Bacteroides Fragilis* is also isolated. The natural resistance of *B. fragilis* to some antimicrobials causes increased bacteremia mortality (Jeverica et al., 2019).

Blood culture remains the gold standard for detecting bacteremia and fungemia. In recent years, the rate of pathogen detection in blood cultures has increased with many developments. These; development of new broths, the addition of growth factors, and neutralization of growth inhibitors/metabolic products/antibiotic residues. Continuously monitored blood culture systems measure the carbon dioxide produced by microorganisms growing in the medium with fluorometric, colorimetric, or manometric sensors. The mean detection time for blood culture positivity is still an average of 15 hours (2.6-127 hours) (Lamy et al., 2016; Venkatesh et al., 2010). The rarity of anaerobic bacteria in bloodstream infections has caused a dilemma in the routine use of anaerobic blood culture bottles. However, the better performance of anaerobic blood culture bottles in the detection of facultative anaerobic bacteria suggested that if not used routinely, it would create a deficiency in the diagnosis of bloodstream infections (Ateş, 2018).

This study aims to interpret the effect of the combined use of aerobic and anaerobic blood culture bottles and the volume of blood taken in the detection of circulatory system infections as soon as possible.

MATERIALS

Our study, which was approved by the ethics committee decision dated February 10, 2016, and numbered 14, was carried out between January 1, 2016, and December 31, 2016. Blood culture sets brought from adult services according to transport rules for one year were evaluated. Blood cultures were identified using BD BACTEC 9240 (Becton Dickinson, USA) as well as standard microbiological methods. We planned our study as descriptive among the blood samples that came in sets, more than one set of the same patient was also evaluated. The volumes of the blood samples were measured and recorded by comparing them with the previously labeled BACTEC Plus Aerobic/F and BACTEC Plus/Anaerobic blood culture bottles.

Evaluation of Reproduction

Blood culture sets consisting of 1 aerobic and 1 anaerobic bottle sent to the microbiology laboratory were placed in the BD BACTEC 9240 (Becton Dickinson, USA) device after registration. The bottles

that gave a positive signal during the seven-day incubation period were removed from the device by recording the positivity time. After the plastic top caps were wiped with alcohol, 1-2 ml of the blood-water mixture was aspirated from the bottle with the help of a sterile syringe. Preparat for Gram stain in a class 2 biosafety cabinet with some of the blood sample taken and the remaining amount was subcultured to 5% Sheep Blood Agar, Chocolate Agar, Eosin Methylene-Blue Agar (EMBA), and Sabouraud Dextrose Agar (SDA) and incubated overnight at 35 °C in an aerobic environment. In addition, anaerobic bottles with positive signals were inoculated into an anaerobic medium and incubated at 35 °C for 48-72 hours in a jar with a gas pack added. At the end of the incubation period, vials that did not receive a growth signal were terminated as "negative" by the device and checked under aseptic conditions.

Evaluation of Results

The growth and growth times of the isolates grown in aerobic and anaerobic blood culture bottles were compared. Bacteria detected in blood samples were evaluated in the light of clinical information in the information system of the patients and other laboratory data.

Statistical Methods

In this descriptive study, SPSS 16.0 (Statistical Package for Social Sciences) package program was used in the analysis of the data. Mean, standard deviation, and percentage distributions are given as descriptive statistics. The Chi-Square test was applied in the comparison of non-numerical variables. Independent variables t-test was used to compare binary variables with numerical data. Obtained results were evaluated at a 95% ($P<0.05$) significance level.

RESULTS

In our study, 8178 out of a total of 11234 blood culture bottles were evaluated. A positive signal was detected in 1084 (11.9%) of 8178 blood culture bottles. 54% of the evaluated samples came from intensive care units (Fig. 1). False positives were observed in 19 (0.2%) blood culture bottles that gave a positive signal, and false negatives were observed in 6 (0.06%) of them. There was no growth in a total of 7217 blood culture bottles (Table 1). Out of a total of 1084 isolates, 635 were clinically significant and 449 were considered contaminants (contamination rate 5.5%). The samples were taken from internal medicine, anesthesia care, internal medicine intensive care, cardiology intensive care, neurology intensive care and neurosurgery intensive care services.

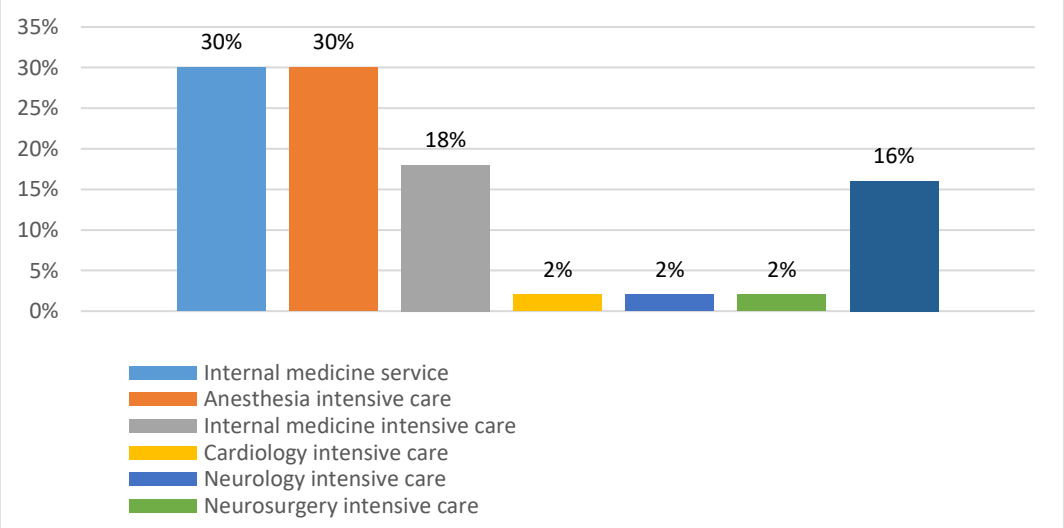

Figure 1. Percentage distribution of blood cultures by services

Most of the contaminating bacteria were coagulase-negative staphylococci, while *Bacillus*, *Corynebacterium*, and *viridans Streptococcus* were the other contaminants.The main pathogens considered as causative agents, coagulase-negative *Staphylococc*i 114 (18%), *S. aureus* 108 (17.1%), *Klebsiella spp* 86 (13.6%), *E. coli* 63 (9.9%), yeast 45 (7.1%), *Acinetobacter spp* was 43 (6.8%). In addition, 488 (77%) of 635 clinically important microorganisms grown in aerobic and anaerobic blood culture bottles were detected in both bottles, 77 (12%) in

the aerobic bottle only, and 70 (11%) only in the anaerobic bottle (Table 1). The clinically significant growth rate in blood cultures was 6.3%. While the false positive rate was 0.2%, the false-negative rate was 0.06%. In 11% of clinically significant isolates grown in blood culture bottles, growth was observed only in the anaerobic bottle.

Table 1. Microorganisms are Grown in Blood Cultures and Distribution of Contaminating Bacteria

Microorganism	Isolates	%
Gram-positive	730	67.3
Coagulase Negative *Staphylococcus*	519	47.8
S.aureus	108	17.1
S.pneumoniae	2	0.1
Viridans streptokok	19	1.7
Enterococcus faecalis	22	2
Enterococcus faecium	29	2.6
Bacillus	13	1.1
Corynebacterium	18	1.6
Enterobacteriaceae	201	18.5
Escherichia coli	63	9.9
Klebsiella sp	86	13.6
Enterobacter cloacae	7	0.6
Proteus sp	6	0.5
Salmonella sp	2	0.1
Serratia marcescens	37	3.4
***Non-Fermenting* Gram-Negative Bacilli (NFGNB)**	102	9.4
Pseudomonas sp	24	2.2
Other NFGNB	19	1.7
Acinetobacter sp	43	6.8
Stenotrophomonas maltophilia	16	1.4
Yeast	45	7.1
Candida albicans	12	1.1
Candida glabrata	11	1
Candida parapsilosis	7	0.6
Candida tropicalis	6	0.5
Candida krusei	2	0.1
Candida sp	3	0.2
Trichosporon	2	0.1
Geotrichum capitatum	2	0.1
Anaerob	6	0.5
Propionibacterium	5	0.4
Peptostreptococcus	1	0.09

Distribution of contaminant bacteria		
Microorganism	Isolates	%
Corynebacterium	18	4
Bacillus	11	3
Streptococcus	15	3
CNS		
S. epidermidis	186	46
S. hominis	98	24
S. heamolyticus	76	19
S. capitis	29	7
Other CNS	16	4
General evaluation of blood culture results		
Pathogen Reproduction	635	6.4
No Reproduction	7217	88.1
False positivity	19	0.2
False negativity	6	0.06
Microorganism growing in aerobic and anaerobic bottles		
Bottles	Isolates	%
Aerobic and Anaerobic	488	77
Aerobic	77	12
Anaerobic	70	11
Gram stain evaluation from blood culture bottles with a positive signal		
Gram positive	**Gram stain/Total**	**%**
CNS	519/519	100
S.aureus	108/108	100
Enterococcus	48/51	94.1
Streptococcus	17/21	80.9
Enterobacteriaceae		
E.coli	59/63	93.6
Klebsiella sp	77/86	89.5
Enterobacter cloacae	6/7	85.7
Proteus sp	6/6	100
Salmonella sp	2/2	100
Serratia marcescens	35/37	94.5
NFGNB		
Pseudomonas sp	23/24	95.8
Other NFGNB		
Acinetobacter sp	20/43	46.5
S. maltophilia	16/16	100
Yeast	45/45	100

Gram-positive cocci, non-fermenting Gram-negative bacillus, gram-positive bacillus, and most yeast growths were detected earlier in the aerobic flask than in the anaerobic flask. In the *Enterobacteriaceae* group, *E. coli*, *Klebsiella spp* was detected earlier in the anaerobic bottle than in the aerobic bottle, while Serratia marcescens isolates were detected earlier in the aerobic bottle. No significant difference was

found between the two vials for *Proteus spp*, *Salmonella spp*, and *Enterobacter cloaca*. The mean positive signal times were 18.5 and 20.9 hours for the aerobic and anaerobic bottles, respectively. 91.7% and 92.8% of clinically significant bacterial and fungal isolates were detected in the first 24 hours of incubation, respectively, and 97.2% and 94.9% in the first 72 hours (Table 2). A significant increase was found between increasing sample volume in blood culture bottles and the number of isolates detected ($p < 0.05$). However, there was no significant relationship between blood culture volume and positive signal duration (Fig. 2).

Table 2. Comparison of Growth Times of İsolates Grown in Aerobic and Anaerobic Blood Culture Bottles

Microorganism	Aerobic Bottle				Anaerobic Bottle			
	Reproduction the time (hour)				Reproduction the time (hour)			
	İsolate	Average	Median	Min-Max	İsolate	Average	Median	Min-Max
Gram-positive cocci	245	20.1	18.1	0.5-130.8	254	21.8	22.5	1.05-135.6
S.aureus	98	18	12.3	1.4-93.3	104	19	16.8	2.2-64.6
CNS	100	23.7	19.2	0.3-130	98	24.9	21.4	1.05-129.2
Pneumococcus	2	23.3	23.3	23.3-23.3	2	22.1	22.1	22.1-22.1
Other Streptococci	4	16.8	17.7	10.9-21.9	4	45.2	27.4	1.8-124.8
Enterococcus	41	16.1	13.8	3.2-42.7	46	19.5	12.4	1.05-135.6
Enterobacteriacae	177	16.5	9.6	0.6-111.7	194	15.1	11.2	0.75-150.5
E. coli	54	18.1	8.2	0.8-111.7	63	17.3	13.2	1.1-150.5
Klebsiella spp	77	18.1	9.8	0.6-93.6	81	13.1	10.6	0.75-62.6
E. cloacae	7	5.9	3.9	1.9-8.9	6	7.9	7.7	2.1-13.9
Proteus spp	6	3.8	3.3	1.6-6.5	6	3.2	2.7	2.9-5.5
Salmonella spp	2	31.2	31.2	31.2-31.2	2	45.7	45.7	45.7-45.7
Serratia marcescens	31	13.6	12.2	0.9-54.7	36	17.1	11.3	1.05-133.5
NFGNB	97	13.6	9.9	2.3-39.1	69	25.9	17.4	1.5-125.9
Pseudomonas spp	24	12.4	6.6	3.9-26.7	16	19.9	19.9	3.5-35.3
Non-*Pseudomonas* non-fermenter	18	28.1	27.4	26.1-31.5	13	42.6	37.1	32.4-58.3
Acinetobacter spp	40	11.3	8.8	2.3-39.1	27	43.6	18.4	3.6-46.2
Stenotrophomonas maltophilia	15	17	9.8	5.1-38.1	13	33.3	14.6	1.5-125.9
Bacillus	2	49	37.4	17.5-95.9	2	45.1	45.7	16.9-72
Yeast	44	22.8	22.1	1.5-50.1	33	22	18.6	10.9-47.1
Anaerob	0				6	95.9	143.9	15.9-150

*Fisher's Exact Test

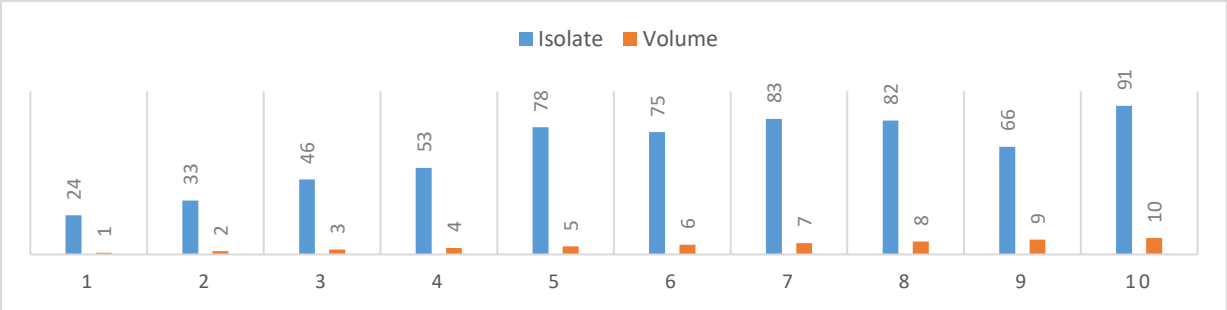

Figure 2. Average sample volume and number of ısolates detected ın blood culture bottles

DISCUSSION

Although mortality rates due to circulatory system infections vary from region to region, it varies between 12-80% and an average of 35% (Paolucci et al., 2010). Blood cultures are the gold standard in the diagnosis of sepsis, but results are obtained in a relatively long time (Bloos et al., 2012; Pletz et al., 2011). Continuously monitored blood culture systems have been used in many clinical microbiology laboratories for the early detection of microorganisms in the blood for nearly 50 years. Samples are kept in the system for up to five or seven days unless the instrument signals (Obara et al., 2011; Tsalik et al., 2010). Because of the delay in identifying pathogens from the growing blood culture and performing antibiotic susceptibility tests, clinicians often make the diagnosis of sepsis according to clinical symptoms and start antibiotic treatment according to the clinical situation (Wolk & Dunne, 2011).

The sensitivity of blood cultures is low in bacteremias caused by slow and hard-growing organisms, and those receiving antibiotic treatment before blood collection (Gaibani et al., 2009). In addition, the positivity rate is affected by the amount of blood taken, antibiotic treatment, taking it under sterile conditions, and transport conditions (Bloos et al., 2012). Similar to our study (11.9%), the rate of blood culture positivity varies between 8.6-32.95% in studies conducted in Turkiye (Gülmez & Gür, 2012; Yiş, 2015). In studies conducted outside of Turkiye, this rate is between 5.6% and 12% (Luzzaro et al., 2002; Mehdinejad et al., 2009). It is thought that there are reasons such as different results, clinical conditions of the patients, variability of age groups, insufficient blood collection, blood culture not being taken at the appropriate time, and the patient's use of antibiotics (Klouche & Schröder, 2008). In studies originating from Turkey, the rates of Gram-positive and Gram-negative bacteria isolated from blood cultures Çetin et al. 67.3%- 29.4%, Müderris et al. 42.9%- 57.1%, Duman et al. They found it to be 68.5%- 31.5% (Çetin et al., 2014; Duman, 2011; Müderris et al., 2019).

It is thought that Gram-negative bacteria detected in our study and among the studies are in the first place, and these different rates differ according to the type and size of the hospital, the rates of bacteremia due to the catheter. In studies conducted to detect bacteremia agents, it has been reported that fungi are isolated at rates ranging from 3-20%. In our study, this rate was determined as 7.1%. It is thought that reasons such as prolonged hospitalization, intensive use of antibiotics, and the use of catheters play a role in the detection of fungi at such a high rate. As in our study, most of the Gram-positive bacteria isolated from blood cultures in other studies are S. aureus and CNS (Abebaw Shiferaw et al., 2018; Şirin et al., 2017).

Our study suggested that the use of anaerobic bottles is not limited to the detection of obligate anaerobic bacteria, but showed that the use of BACTEC Plus Aerobic/F and BACTEC Plus Anaerobic/F blood culture bottle combination allows the detection of aerobic microorganisms grown in anaerobic.

Limitations

Considering that ideally, the rate of contaminated blood culture should not exceed 2-3%, the rate of contamination was high in our hospital. The reason for this was thought to be problems related to the non-compliance with the aseptic conditions in the blood collection technique and the education level of the personnel who took the blood. The appropriate blood volume is 10 ml per bottle according to CLSI recommendations. In our study, the average blood culture volume from the wards was 4-5 ml per bottle. The higher yield of blood cultures with lower blood volume may be related to population differences and blood culture collection time. In addition to our study, PCR was not considered an appropriate method because of the high cost of PCR-based testing compared to traditional culture methods, and the need for experienced personnel and high-level equipment.

CONCLUSION

Based on positive signal duration and agent detection rates in blood cultures, we hope that the combination of aerobic and anaerobic blood culture bottles will be used more efficiently as a crucial diagnostic tool. It was concluded that the use of aerobic and anaerobic blood culture bottles and blood volume together is very valuable in the rapid detection of circulatory system infections.

Ethics Committee Approval

This study was started with the decision of Eskişehir Osmangazi University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee dated 10.02.2016 and numbered 14.

Conflict of Interest
There is no conflict of interest between the authors.

Author Contributions
SY took charge of the identification of isolates performed data collection and analysis, antimicrobial activity data, and statistical analysis. GD was involved in data collection and analysis of data and proofread the manuscript. BI analyzed the antimicrobial activity data and prepared the manuscript.

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