Characteristics of Microorganisms Isolated from Blood Cultures at Nine University Hospitals in Korea during 2009

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Background: Blood culture is important for determining the etiologic agents of bacteremia and fungemia. Analyses of blood culture results and antimicrobial susceptibility can provide clinicians with relevant information for the empirical treatment of patients. The present study was conducted to assess the frequencies and antimicrobial resistance patterns of clinically important microorganisms from nine hospitals.

Methods: Data including microbiological isolates and corresponding antimicrobial susceptibility test results were collected during 2009 from nine and five university hospitals, respectively. Microorganism identification was based on conventional methods. Antimicrobial susceptibility was tested using the VITEK II system or the Clinical and Laboratory Standards Institute disk diffusion method.

Results: Of 397,602 blood specimens cultured from nine hospitals, 34,708 (8.7%) were positive for microorganisms. Excluding coagulase-negative Staphylococci (CoNS), *Escherichia coli* was the most com-

INTRODUCTION

The isolation of bacteria from blood cultures is usually indicative of a serious invasive infection requiring urgent antimicrobial therapy. Different microorganisms have different antimicrobial susceptibilities and successful treatment is dependent on the prompt administration of the proper antimicrobial agents. Throughout the 1960s and 1970s, Gram-negative microor-

Received 1 December, 2010, Revised 3 March, 2011 Accepted 27 April, 2011 mon isolate (13.5%), followed by *Staphylococcus aur*eus (11.5%), *Klebsiella pneumoniae* (6.5%) and *Enterococcus faecium* (3.4%). The isolation rate of CoNS was 23.6%, while that of ceftazidime-resistant *E. coli* showed geographic differences ranging from 11% to 28%. Among the Gram-negative isolates, *A. baumannii* displayed the highest levels of resistance. The total isolation rate of the *Candida* species increased compared to the previous reported rate in Korea.

Conclusion: Among the isolates, CoNS was the most common, followed by *E. coli* and *S. aureus*. The gradual increase in the prevalence of extended-spectrum β -lactamase (ESBL) producers has contributed to the increase in multi-drug resistance among bacterial isolates from bloodstream infections. (Korean J Clin Microbiol 2011;14:48-54)

Key Words: Blood culture, Bacteremia, Antimicrobial susceptibility, Fungemia

ganisms were most frequently isolated from patients with nosocomial bloodstream infections (BSI). Since then, the number of infections due to Gram-positive microorganisms has been increasing [1-3]. In addition, antibiotic resistance rates have been rising for all predominant microorganisms, including *Staphylococcus aureus* [2,4], coagulase-negative staphylococci (CoNS) [5], Enterococci [6], and Gram-negative pathogens [3,7,8]. In the face of emerging multi-resistant microorganisms, antimicrobial prophylaxis and treatment have become increasingly difficult. Additionally, timely and accurate epidemiologic information is needed to guide the choice of an appropriate empirical therapy. *Candida* BSIs have increased due to the use of broad-spectrum antibiotics and the increasing number of immunocompromised patients. Analyses of *Candida* BSIs have shown trends toward the selection for non-*albicans Candida* spe-

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cies, some of which are difficult to treat with first-generation azoles [9,10].

Blood culture is important for the determination of the etiologic agent of bacteremia or fungemia. Analysis of blood culture results and antimicrobial susceptibility trends can provide clinicians with relevant information for the empirical treatment of patients with sepsis. Although there are data on blood culture from several hospitals in Korea, it is hard to acquire multicenter data encompassing various regions in Korea. This study was conducted to assess the frequency of medically important microorganisms and the antimicrobial susceptibilities of common pathogens.

MATERIALS AND METHODS

1. Study design

The surveillance network included data acquired from January 2009 to December 2009 at 9 university hospitals of various sizes (range, $700 \sim 2,700$ beds) distributed throughout Korea (Asan Medical Center; Samsung Medical Center; Seoul National University Hospital; Gyeongsang National University Hospital; Inje University Paik Hospital; Chungnam National University Hospital; Dongsan Medical Hospital; Wonkwang University Hospital; and Kangdong Sacred Heart Hospital). Data regarding each microbiological isolate and corresponding antimicrobial susceptibility test results were collected using a standardized report form. The sizes of the intensive care units, emergency departments and disease distribution were outside the scope of this study.

2. Microbiological methods

Blood cultures were processed at the participating hospitals. The identification of blood isolates and susceptibility testing were performed according to the routine methods in use at the affiliated laboratories. All microbiological methods were consistent with the current Clinical and Laboratory Standards Institute (CLSI) guidelines [11]. Data from participating hospitals were used for analysis; however, the number of tested isolates for each antimicrobial agent varied because the participating laboratories did not have same susceptibility test panels. Although the bacteriologic profiles from blood cultures were obtained from 9 participating hospitals, *in vitro* antibiogram data for the bacterial isolates were available from only 5 out of 9 hospital; Inje University Paik Hospital; Chungnam National University Hospital; Wonkwang University Hospital).

1) Isolate frequency: The frequency of several commonly isolated microorganisms was determined. Among the Gram-positive cocci, the frequencies of *S. aureus, Enterococcus faecium*, and CoNS including *Staphylococcus epidermidis* were reviewed. *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa* and *Acinetobacter baumanii* were included as Gram-negative bacilli. For yeast, the frequencies of *Candida albicans*, *Candida tropicalis, Candida parapsilosis*, and *Candida glabrata* were investigated.

2) Antimicrobial susceptibility test: The antimicrobial resistance rates for several medically important microorganisms (*S. aureus, E. faecium, Enterococcus faecalis, E. coli, K. pneumoniae, A. baumannii* and *P. aeruginosa*) as well as *S. epidermidis* were included.

RESULTS

Of 397,602 blood specimens cultured from 9 laboratories, 34,708 (8.7%) were positive for the microorganisms tested. The average positive blood culture rate at the 9 university hospitals was 8.6% (95% CI, $7.5 \sim 9.7\%$), whereas the polymicrobial infection rate was as low as 0.3% (95% CI, $0.2 \sim 0.4\%$).

1. The frequency of Gram-positive cocci

The total number of isolates varied according to the hospital, and may have been affected by the number of samples ordered. The average number of isolates was 4,401 (SD 2,456; range, 1.128~10,132). Among the approximately 35,000 isolates, the frequencies of *S. aureus* and *E. faecium* were 11.7% (95% CI, 9.6~13.8%) and 3.4% (95% CI, $1.9 \sim 5.0\%$), respectively (Fig. 1). All but one institution showed more frequent isolation of *E. faecium* than *E. faecalis* (data not shown). CoNS isolated from 23.6% (95% CI, $18.7 \sim 28.4\%$) of samples. Among CoNS, *S. epidermidis* was most common at 12.1% (95% CI, $9.6 \sim 14.6\%$), followed by *Staphylococcus hominis* at 3.9% (95% CI, $2.3 \sim 5.5\%$). Three institutions had a CoNS isolation frequency greater than 30%.

2. The frequency of Gram-negative bacilli

The most common Gram-negative microorganisms were *E.* coli (13.5% [95% CI, 11.6~15.3%]) and *K. pneumoniae* (6.5% [95% CI, $5.3 \sim 7.7\%$]). Common nosocomial pathogens such as *A. baumannii* and *P. aeruginosa* were isolated from 2.6% (95% CI, $1.8 \sim 3.4\%$) and 2.5% (95% CI, $1.6 \sim 3.3\%$) of samples, respectively (Fig. 1).

3. The frequency of yeasts

C. albicans was the most common among the yeasts accounting for 2.3% (95% CI, $1.6 \sim 3.6\%$) of the total isolates (Fig. 2). The frequencies of *C. parapsilosis*, *C. tropicalis*, and *C. glabrata* were 1.9% (95% CI, $0.6 \sim 3.1\%$), 1.4% (95% CI, $1.0 \sim 1.9\%$), and 0.6% (95% CI, $0.3 \sim 0.9\%$), respectively (Fig. 2). At one institution, the isolation frequency of *C. albicans* was 6.1% and in another institution that of *C. parapsilosis* was 6.0%.

4. Antimicrobial resistance

1) Gram-positive cocci: The antimicrobial resistance levels for the most common Gram-positive microorganisms causing BSIs are shown in Table 1. Resistance to methicillin was detected in 69.8% of *S. aureus* and 84.7% of *S. epidermidis* isolates. The highest proportion of methicillin resistance in *S. aureus* isolates (82.2%) was seen in the central region

(Daejeon). Vancomycin resistance was not detected in either *S. aureus* or *S. epidermidis* isolates.

Ampicillin resistance rates for *E. faecalis* and *E. faecium* were 14.2% and 91.2%, respectively. Notably, the rates of vancomycin resistance were highly correlated with enterococcal species. The proportion of resistance to vancomycin was 28.6% in *E. faecium* isolates and 0% in *E. faecalis* isolates. Geographic



Fig. 1. The isolation frequencies of common bacteria from 9 hospitals. A, Asan Medical Center; B, Samsung Medical Center; C, Seoul National University Hospital; D, Gyeongsang National University Hospital; E, Inje University Paik Hospital; F, Chungnam National University Hospital; G, Dongsan Medical Hospital; H, Wonkwang University Hospital; I, Kangdong Sacred Heart Hospital.

variation of vancomycin resistance in *E. faecium* was significant and ranged from 9% in the southwest (Iksan) to 46% in the southeast (Busan), with the central region (Seoul and Daejeon) having an intermediate level $(18 \sim 35\%)$ (data not shown). *Streptococcus pneumoniae* isolates exhibited high proportions of resistance to tetracycline (68.1%) and erythromycin (61.5%). While 20.9% and 24.6% of isolates were resistant to penicillin and trimethoprim-sulfamethozaxole, respectively, cefotaxime and levofloxacin displayed good activity.

2) Gram-negative rods: Antimicrobial resistance levels for the most common Gram-negative microorganisms causing BSIs are



Fig. 2. The isolation frequencies of common yeasts from 9 hospitals. See Fig. 2 for designations for each hospital $(A \sim H)$.

 Table 1. Rates of antibiotic resistance among the most common Gram-positive bacteria causing bloodstream infections from 5 Korean hospitals in 2009

	Staphylococcus aureus		Staphylococcus epidermidis		Enterococcus faecium		Enterococcus faecalis		Streptococcus pneumoniae	
	Ν	% resistance	Ν	% resistance	Ν	% resistance	Ν	% resistance	Ν	% resistance
Ampicillin	ND	NA	ND	NA	336	91.2	186	14.2	ND	NA
Penicillin	1121	95.4	1032	96.8	336	92.1	186	15.7	49	20.9
Clindamycin	1121	63.8	1032	65.9	ND	NA	ND	NA	ND	NA
Oxacillin	1072	69.8	1032	84.7	ND	NA	ND	NA	ND	NA
QNP-DFP	1072	0.2	1032	0.1	ND	NA	ND	NA	ND	NA
Cefotaxime*	ND	NA	ND	NA	ND	NA	ND	NA	52	7.3
Cefotaxime [†]	ND	NA	ND	NA	ND	NA	ND	NA	52	5.4
Erythromycin	1121	61.0	1032	71.3	ND	NA	ND	NA	59	61.5
Ciprofloxacin	1121	56.4	1032	58.8	ND	NA	ND	NA	ND	NA
Levofloxacin	731	62.4	656	26.2	ND	NA	ND	NA	59	7.9
Gentamicin	947	61.4	1032	63.7	ND	NA	ND	NA	ND	NA
HL Gentamicin	ND	NA	ND	NA	325	49.2	186	37.9	ND	NA
HL Streptomycin	ND	NA	ND	NA	325	8.0	186	16.9	ND	NA
Rifampin	502	2.8	1032	16.2	ND	NA	ND	NA	ND	NA
Tetracycline	1121	55.8	1032	22.9	ND	NA	ND	NA	59	68.1
TMP-SMX	502	7.3	522	49.7	ND	NA	ND	NA	34	24.6
Vancomycin	1072	0.0	1032	0.0	336	28.6	186	0.0	52	0.0

*Meningitis, CLSI-recommended resistant MIC breakpoint $2 \ge \mu g/mL$, [†]Non-meningitis, CLSI-recommended resistant MIC breakpoint $4 \ge \mu g/mL$.

Abbreviations: ND, not done; NA, not applicable; QNP-DFP, quinupristin-dalfopristin; HL, high-level; TMP-SMX, trimethoprim-sulfamethoxazole. shown in Table 2. *E. coli* isolates displayed relatively high resistance to ampicillin (63.4%), piperacillin (44.2%), trimethoprim-sulfamethoxazole (37.0%) and ciprofloxacin (36.6%). However, all cephalosporins and gentamicin displayed relatively good activity. Of the *K. pneumoniae* isolates, 96.8% and 71.5% were resistant to ampicillin and piperacillin, respectively. Only imipenem and meropenem demonstrated *in vitro* activity in at least 90% of *K. pneumoniae* isolates. Ceftazidime resistance was found in 19.9% of *E. coli* isolates and in 24.2% of *K. pneumoniae* isolates. Among the Gram-negative isolates, *A. baumannii* displayed the highest levels of resistance. A high proportion of *A. baumannii* isolates were resistant to ceftazidime (56.4%), gentamicin (61.2%) and ciprofloxacin (62.0%). A total of 34.2% *A. baumannii* isolates showed resistance to imipenem and 54.4% were resistant to meropenem. Of the *P. aeruginosa* isolates, 21.5% were resistant to ceftazidime and 25.0% were resistant to imipenem.

DISCUSSION

The positive blood culture rate ranged between 6.4% and 11.9% in this study, which is similar to or higher than that reported by single-institution studies in Korea ($4.6 \sim 9.6\%$) [12-14]. The positive rate in blood culture varies with multiple factors such as patient characteristics, culture methodology and the frequency with which blood cultures are ordered by clinicians.

Table 2. Rates of antibiotic resistance among the most common Gram-negative rods causing bloodstream infections from 5 Korean hospitals in 2009

	Escherichia coli		Klebsiella pneumoniae		Acinetoba	cter baumannii	Pseudomonas aeruginosa	
	N	% resistance	Ν	% resistance	Ν	% resistance	Ν	% resistance
Ampicillin	1537	63.4	702	96.8	ND	NA	ND	NA
Amoxicillin-Clavulanate	ND	NA	702	17.8	ND	NA	ND	NA
Piperacillin	721	44.2	597	71.5	200	57.2	263	26.2
Piperacillin-Tazobactam	1129	10.2	736	12.5	200	49.9	263	20.6
Ticarcillin	ND	NA	ND	NA	ND	NA	250	32.9
Ticarcilin-Clavulanate	ND	NA	ND	NA	151	53.1	ND	NA
Cefazolin	832	23.9	394	30.4	ND	NA	ND	NA
Cefoxitin	ND	NA	736	14.0	ND	NA	ND	NA
Cefotaxime	1537	19.1	736	27.2	ND	NA	ND	NA
Ceftazidime	1129	19.9	736	24.2	226	56.4	250	21.5
Cefepime	1113	19.7	736	26.7	226	55.8	263	18.1
Imipenem	1456	0.2	702	0.4	226	34.2	250	25.0
Meropenem	1456	0.1	702	0.7	226	54.4	250	19.0
Aztreonam	ND	NA	736	28.0	ND	NA	250	20.9
Ciprofloxacin	913	36.6	394	17.5	207	62.0	263	18.8
Levofloxacin	ND	NA	394	13.4	226	43.4	157	32.5
Gentamicin	1537	27.0	736	19.4	226	61.2	263	13.3
Amikacin	ND	NA	736	13.7	ND	NA	263	6.7
Tobramycin	1537	14.0	736	19.8	226	47.2	263	11.4
TMP-SMX	1032	37.0	509	23.3	ND	NA	126	98.4

Abbreviations: See Table 1.

Table 3. Rank order of microorganisms or microorganism groups most frequently isolated from blood samples

Rank	Study (period)								
	This study (2009)	Kang et al [13] (2003~2007)	Ahn et al [14] (2002~2005)	Koh et al [12] (1994~2003)	Weinstein et al [22] (1990s)	Cockerill et al [15] (1996~1997)			
1	CoNS	CoNS	CoNS	CoNS	S. aureus	S. aureus			
2	E. coli	E. coli	E. coli	E. coli	E. coli	E. coli			
3	S. aureus	S. aureus	S. aureus	S. aureus	CoNS	CoNS			
4	K. pneumoniae	K. pneumoniae	S. maltophilia	SVG	K. pneumoniae	Enterococci			
5	E. faecium	S. pneumoniae	S. marcescens	Enterococci	Enterococci	C. albicans			

Abbreviations: CoNS, coagulase-negative staphylococci; S. aureus, Staphylococcus aureus; E. coli, Escherichia coli; K. pneumoniae, Klebsiella pneumoniae; S. maltophilia, Stenotrophomonas maltophilia; SVG, Streptococcus viridans group; E. faecium, Enterococcus faecium; S. marcescens, Serratia marcescens; C. albicans, Candida albicans.

The relative frequencies of isolates among approximately 35,000 microorganisms isolated from blood culture were analyzed. Excluding CoNS, *E. coli* (13.5%) was the most common isolate, followed by *S. aureus* (11.5%), and *K. pneumoniae* (6.5%). *E. faecium*, approximately 30% of which was vancomycin-resistant Enterococci, accounted for 3.4% of all isolates. The nonfermentive Gram-negative rods, *A. baumanii* and *P. aeruginosa*, had frequencies of 2.6% and 2.5%, respectively. Among the isolates, CoNS (23.6%) was the most frequently isolated microorganism and the difference between the highest and the lowest isolation frequencies was 2.5-fold.

The frequencies of isolates differ according to the study (Table 3). In Korea, Koh et al. [12] reported CoNS, *E. coli, S. aureus*, alpha-hemolytic streptococci, Enterococci, and *K. pneumoniae* in decreasing order. In another study, Ahn et al. [14] listed CoNS, *E. coli*, and *S. aureus*, followed by *Stenotrophomonas maltophilia* and *Serratia marcescens*. Cockerill et al. [15] analyzed data from 1996~1997 in the United States and reported *S. aureus*, *E. coli*, CoNS, Enterococci, *C. albicans*, and *P. aeruginosa* in decreasing order. Isolate frequency can be affected by skin disinfection methods, composition of the patient group as well as the number of blood culture.

According to the data, obligate anaerobes were rarely isolated and thus were excluded in this study. The reason for the low incidence of obligate anaerobic bacteremia might be the prophylactic usage of antibiotics before surgery as well as wide use of broad-spectrum antibiotics [16].

With the increased use of aggressive interventions that disrupt the integrity of skin or mucosa and vascular catheters, the likelihood that CoNS will cause infections is increasing. CoNS grow slowly or grow in only one of several replicate cultures if it is a skin contaminant [17-19]. Given the high likelihood that isolation of CoNS from blood cultures is usually indicative of contamination, determining the likelihood of true bacteremia can be challenging for clinicians, and this is beyond the scope of this study.

The use of broad-spectrum antibiotics or immunosuppressants, transplantation, and aging are risk factors for fungal infections [20-22]. As the mortality rate of fungemia is very high, it should be reported with urgency in order for timely treatment with antifungal agents. The most common yeasts in this study were *C. albicans*, followed by *C. parapsilosis*, *C. tropicalis*, and *C. glabrata*. The total isolation rate of *Candida* spp. exceeded 6%, which is higher than the 2.8% reported by Ahn et al. [14]. Lee et al. [21] reported the frequencies of yeasts such as *C. albicans* (49%), *C. parapsilosis* (22%), *C. tropicalis* (14%), and *C. glabrata* (11%) in a multicenter study; results that are similar to those from our current study.

The rate of resistance to methicillin among *S. aureus* (\sim 70%) was consistent with recent data from other studies in Korea [14,23]. Ampicillin resistance in *E. faecalis* found in our study is relatively high (14.2%) compared to that in a previous study in Korea (\sim 0%). We observed that the rate of resistance to ampicillin in *E. faecuum* infections was as high as 90% and was

comparable to rates reported in recent studies from Korea [12,24]. In our study, the prevalence of resistance to vancomycin among *E. faecium* isolates (25%) was similar to the prevalence previously reported in Korea (29 \sim 33%) [12,23]. The high rates of resistance to ampicillin and vancomycin should be considered in the empirical treatment of *E. faecium*.

Although the number of *S. pneumoniae* isolates in this study was small, the prevalence of penicillin resistance was noticeably lower in this study (21%) in comparison to 55% reported by Song et al. [25]. In January 2008, the CLSI published new *S. pneumoniae* breakpoints for penicillin. Many studies that applied the new CLSI guidelines reported an increase in the penicillin susceptibility of *S. pneumoniae* strains isolated from blood [26,27].

Increases in the prevalence of extended-spectrum β -lactamase (ESBL)-producing E. coli and K. pneumoniae have been reported in Korea [12,28]. In this study, when the resistance to ceftazidime was used as a marker for the potential presence of ESBL, 20% of E. coli and 24% of K. pneumoniae isolates were potential carriers of these enzymes. According to a previous study that included 12 hospitals [28], the proportion of ESBLproducers was 9.1% (range, 2.0~19.6%) of the E. coli and 29.2% (range, 10.0~60.8%) of the K. pneumoniae isolates. Koh et al. [12] reported a wide range of cefotaxime resistance for E. coli and K. pneumoniae isolates depending on different survey years $(2 \sim 28\%)$ and $4 \sim 31\%$, respectively). The incidence of ESBL-producing isolates varies according to country, region and even hospital. We also found marked geographic differences in the occurrence of ceftazidime resistance, ranging from 11% to 28% of E. coli isolates and from 12% to 51% of K. pneumoniae isolates, respectively.

In conclusion, the frequency of common pathogens was reported based on multi-institutional data from 2009. These data suggest the need to review the possibility of an outbreak of some pathogens such as *C. albicans* and *C. parapsilosis*. Among the isolates, CoNS was the most common, followed by *E. coli* and *S. aureus*. The high prevalence of ESBLs has contributed to the finding of multi-drug resistance among *K. penumoniae* and *E. coli*. Furthermore, *A. baumannii* and *P. aeruginosa* isolates displaying resistance to many antibiotics including carbapenem make the selection of optimal antibiotics difficult. Adequate management of infections due to these multi-drug resistant pathogens requires knowledge of microbiological epidemiology and practices to control their spread.

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=국문초록=

2009년 9개 대학병원의 혈액배양에서 흔히 분리된 균주 및 항균제 내성 양상

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배경: 혈액배양은 균혈증과 진균혈증의 원인균을 밝히는데 필수적인 방법으로 원인 균주와 항균제 감수성 결과를 파악 함으로써 임상에서 적절하고 경험적인 치료법을 선택할 수 있도록 유용한 정보를 제공한다. 이에 본 연구에서는 9개 병원을 대상으로 임상적으로 중요한 세균들의 분리율과 항균제 감수성 양상에 대하여 알아보고자 하였다.

방법: 2009년 1월부터 12월까지 1년간 9개 병원에서 혈액 배양이 의뢰된 검체를 대상으로 혈액배양 양성으로 나온 군종 의 결과와 이 중 5개 병원에서 제공한 항균제 감수성 결과를 분석하였다. 혈액배양은 통상적인 혈액배양법을 시행하였고 균의 동정 및 항균제 감수성 검사는 VITEK II 장비 또는 Clinical and Laboratory Standards Institute 디스크법으로 시행하였 다.

결과: 혈액배양이 의뢰된 총 검체수는 397,602이었고 이 중 34,708 (8.7%)는 배양 결과 양성 균주를 보였다. 분리된 균주 중에 coagulase negative Staphylococci (CoNS)를 제외하였을 때 가장 흔한 병원균은 *Escherichia coli* (13.5%)였고, 다음으로 *Staphylococcus aureus* (11.5%), *Klebsiella pneumoniae* (6.5%), *Enterococcus faecium* (3.4%) 순이었다. 한편, CoNS가 전체 중 23.6%로 가장 흔히 분리되었다. Ceftazidime 내성 *E. coli* 비율이 증가하고 있었으며 지역에 따라 11~28%로 차이를 보였다. 그람 음성 분리주 중 *Acinetobacter baumannii*가 가장 고도 내성을 보였으며 총 *Candida* 종의 분리율은 우리나라 에서 이전에 보고된 바 보다 높아졌다.

결론: 혈액 배양에서 분리된 균주 중에 CoNS가 가장 흔히 분리되었고 다음으로는 E. coli, S. aureus 순이었다. 점차 ESBL 양성 균주가 늘어나고 있는 추세는 균혈증에서 분리되는 다제내성균이 증가하는 데 기여하고 있는 것으로 생각된다. [대한임상미생물학회지 2011;14:48-54]

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