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Original Article

Secular Trends of Species and Antimicrobial Resistance of Blood Isolates in a Tertiary Medical Center for Ten Years: 2003~2012

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Periodic analysis of local epidemiologic data of prevalent pathogens of blood culture can provide clinicians with relevant information to guide empirical antibiotic therapy. In this study, we analyzed a pattern of change of causative microorganisms and antimicrobial resistance at a tertiary medical center in Chungcheong province from 2003 to 2012, retrospectively. Of 70,258 blood specimens cultured, 6,063 (8.6%) were positive. Among the positive isolates, 95.9% were aerobic or facultative anaerobic bacteria, 0.1% were anaerobes, and 3.9% were fungi. Coagulase-negative Staphylococci (CoNS) (32.9%), *Escherichia coli* (16.7%), *Staphylococcus aureus* (9.1%), *Klebsiella pneumoniae* (6.4%), and α-hemolytic *Streptococcus* (5.9%) were commonly isolated bacteria, and *Candida albicans* (1.4%) was the most commonly isolated fungi. *Enterococcus faecium* progressively increased but *Streptococcus pneumoniae*, *Acinetobacter baumannii* and *Proteus* species gradually decreased over a period of 10 years. The multidrug-resistant microorganisms such as methicillin-resistant *S. aureus* (MRSA), vancomycin-resistant enterococci (VRE), cefotaxime-resistant *E. coli*, imipenem-resistant *Pseudomonas aeruginosa* (IRPA) and imipenem-resistant *A. baumannii* (IRAB), were significantly increased. Therefore, there is a need for a more strict control of antibiotics and a more updated guideline for the treatment of bloodstream infection.

Key Words: Blood culture, Species, Antimicrobial susceptibility, Bloodstream infection

INTRODUCTION

Bloodstream infection (BSI) accounts for 10~20% of all nosocomial infections and is eighth leading of mortality in the United States (Wenzel and Edmond, 2001; Martin et al., 2003). Treatment of BSI is often urgent and may have to be performed without definitive identification of the blood microorganisms involved as well as without determination of their antimicrobial resistance. Inadequate empirical therapy of BSI can causes adverse outcomes, including increased morbidity and mortality (Alvarez-Lerma, 1996; Behrendt et al., 1999; Ibrahim et al., 2000), which is usually associated with antimicrobial resistance. In this situation, by knowing the most likely causative microorganisms and their expected resistance patterns, the probability to select an effective antimicrobial agent for empirical treatment can increase. Therefore, timely surveillance studies for the trend of positive isolates from blood culture can provide reliable information to this knowledge base at the national or

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regional level (Yinnon et al., 1997).

Although the annual reports for blood culture were common in the Republic of Korea, studies conducted over ten years are rare (Kim et al., 1985; Kim et al., 1996; Koh et al., 2007; Kim et al., 2012). In recent time, the species of microorganisms isolated from blood have increased and changed due to the increase of immunocompromised patients. In addition, multidrug resistance organisms such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), extended-spectrum β-lactamase (ESBL), imipenem-resistant *Pseudomonas aeruginosa* (IRPA), and IR *Acinetobacter baumannii* (IRAB) have increased worldwide.

In view of the above findings a study conducted to determine the annual changes in frequency of occurrence and antimicrobial resistance of pathogens isolated from blood over a period of ten years from 2003 to 2012 in a university hospital.

MATERIALS AND METHODS

Retrospective clinical study

This is a retrospective study based on laboratory records of ten years from 2003 to 2012 in Chungbuk National University Hospital, Cheongju, Republic of Korea, which is a tertiary teaching hospital with 600 beds and with 173,000 adimissions for years. Only isolates of pathogens repeatedly isolated from patients were included in this study. All patients with suspected bacteremia were examined with two or three times, and a 10 mL blood sample was collected aseptically before the use of antibiotics.

Blood culture

The BacT/ALERT 3D continuous monitoring blood culture system (CMBCS) (bioMérioux Inc. Durham, NC, USA) was used for rapid detection of microorganisms from blood samples. Each 5 mL sample was transferred to BacT/Alert SA aerobic and anaerobic culture vials, respectively. The bottles were loaded in the BacT/Alert 3D instrument. Whenever the machine gave a positive signal, the bottle was removed and subculture was done on blood agar and MacConkey's agar. The identification of organisms was performed by VITEK II automatic analyzer (bioMérieux Inc., Hazelwood, MO, USA) and routine biochemical tests.

Antimicrobial susceptibility testing

Antimicrobial susceptibility testing (AST) was done by VITEK II system or Kirby Bauer disc diffusion method using Muller Hinton agar. Quality control test of AST was performed using standard strains of *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27953, *Staphylococcus aureus* ATCC 25923 and *Enterococcus faecalis* ATCC 29212 as per recommendation of Clinical Laboratory Standard Institute (CLSI, 2012). When vancomycin resistance in gram-positive cocci or imipenem resistance in gram-negative bacilli were observed in VITEK II system or disc diffusion method, vancomycin or imipenem resistance was confirmed by E-test (AB BIODISK, Sweden), additionally.

Statistical analysis

The data was collected from the laboratory information system of hospital and analyzed using Microsoft Excel 7.0 software. Differences in proportions of annual isolation and antimicrobial susceptibilities were compared by a chi-square test using SPSS 19.0. Statistical significance was set for $P<0.05$.

RESULTS

Distribution of blood culture positive isolates

Of 70,258 blood specimens cultured, 6,063 (8.6%) were positive. Among the positive isolates, 95.9% were aerobes or facultative anaerobes, 0.1% were anaerobes, and 3.9% were fungi. Among the pathogens, (except for coagulase-negative staphylococci (CoNS) and gram positive bacilli (GPB) usually considered contaminants), the most common 10 isolates were: *E. coli* (1,010 cases, 16.66%), *S. aureus* (553 cases, 9.12%), *Klebsiella pneumoniae* (390 cases, 6.43%), α-hemolytic streptococci (356 cases, 5.87%), *Enterococcus* spp. (242 cases, 3.99%), *Enterobacter* spp. (119 cases, 1.96%), *P. aeruginosa* (111 cases, 1.83%), *A. baumannii* (92 cases, 1.52%) , *Candida albicans* (85 cases, 1.40%) and *S. pneumoniae* (77 cases, 1.27%) (Table 1).

Table 1. Frequency of blood isolates for ten years

Organisms	Blood isolates	
	Number	%
Gram positive cocci	3,464	57.13
Coagulase negative staphylococci	1,995	32.90
Staphylococcus aureus	553	9.12
α-hemolytic streptococci	356	5.87
Enterococcus spp.	242	3.99
Streptococcus pneumoniae	77	1.27
β-hemolytic streptococci (GA+GB)	65	1.07
Other gram-positive cocci	176	2.90
Gram positive bacilli	252	4.16
Bacillus spp.	190	3.13
Corynebacterium spp.	39	0.64
Other gram positive bacilli	23	0.38
Gram negative cocci	11	0.18
Gram negative bacilli	2,092	34.50
Escherichia coli	1,010	16.66
Klebsiella pneumoniae	390	6.43
Enterobacter spp.	119	1.96
Salmonella spp.	24	0.40
Pseudomonas aeruginosa	111	1.83
Acinetobacter baumannii	92	1.52
Other gram negative bacilli	346	5.70
Anaerobic bacteria	8	0.13
Fungi	236	3.90
Candida albicans	85	1.40
Candida parapsilosis	63	1.03
Candida tropicalis	32	0.53
Other yeast	56	0.92
Total	6,063	100

Abbreviations: GA, group A; GB, group B.

The distribution of bacteria isolated from blood over ten year period of the study has changed. Isolation of *S. pneumoniae*, *A. baumannii* and *Proteus* spp. were gradually decreased and isolation of *Enterococcus faecium* was gradually increased for 10 years. The other bacteria did not significantly change (Table 2).

Antimicrobial resistance pattern of blood culture positive isolates

Trends of antimicrobial resistance of *S. aureus* over ten years were presented in Table 3. Vancomycin resistant *S. aureus* (VRSA) were not observed but MRSA was significantly increased (47.2% to 67.1%, P=0.009) over ten years (Table 3). The average resistance rates for ampicillin in *E. faecalis* and *E. faecium* were 11.1% and 85.3%, respectively. The average vancomycin resistance rate of *E. faecalis* was 2.6% but that of *E. faecium* was 26.4%. Vancomycin-resistance of *E. faecium* (VRE) was significantly increased from 10% to 23.4% over ten years (Table 3). *E. coli* was frequently resistant to ampicillin (58.1%), cefazolin (41.5%), ciprofloxacin (18.3%), and cefotaxime (15.3%) except imipenem (0%). The resistance rate of *E. coli* for cefazolin was significantly increased from 10.2% in 2003-2014 to 47.7% in 2011-2012. In addition, the antimicrobial resistance data of *E. coli* suggests that ESBL was also significantly increased from 6.4% to 26.1% over ten years (Table 3). *K. pneumoniae* was frequently resistant for ampicillin (100%), cefazolin (15.6%), cefotaxime (11.9%), and ciprofloxacin (6.0%) except imipenem (0%). The resistance rate for cefazolin and cefotaxime were increased less than that of *E. coli* during 10 years (Table 3). *P. aeruginosa* was frequently resistant for ciprofloxacin (50.6%), imipenem (36.9%), and ceftazidime (39.2%). The Resistance rate for imipenem was abruptly increased from 16% in 2003-2004 to 56.4% 2009-2010 and decreased to 20% in 2011-2012 (Table 3). *A. baumannii* was frequently resistant to ceftazidime (62.3%), ciprofloxacin (42.5%), and imipenem (31.1%). The resistance rate of *A. baumannii* for imipenem also abruptly increased as *P. aeruginosa* from 14.3% in 2003-2004 to 57.9% in 2011-2012 (Table 3).

DISCUSSION

The present study illustrated the BSI bacterial spectrum and antimicrobial resistance pattern in a university hospital over ten years. The average blood culture positive rate was 8.6% (7.2~12.6%) which is within variable range (4.6~18.5%) reported in other studies in the Republic of Korea (Kim et al., 1985; Kim et al., 1996; Ahn et al., 2006; Koh et al., 2007; Kang et al., 2008; Kim et al., 2012). The varying prevalence of positive rates may be due to different blood culture rates as well as different methodologies used

Table 2. Proportions of common blood isolates for ten years

Microorganisms	Percentage of isolates within the years (Number of isolates)						*P*-value
	2003-4 (n=444)	2005-6 (n=565)	2007-8 (n=730)	2009-10 (n=711)	2011-2 (n=719)	Total (n=3,169)	
S. aureus	15.7 (70)	16.1 (91)	17.7 (129)	19.8 (141)	17.0 (122)	17.5 (553)	0.34
S. pneumoniae	4.3 (19)	3.2 (18)	1.8 (13)	1.5 (11)	2.2 (16)	2.4 (77)	**0.021**
AHS	12.2 (54)	12.6 (71)	12.7 (93)	9.8 (70)	9.5 (68)	11.2 (356)	0.153
GA-BHS	0.9 (4)	0.5 (3)	0.4 (3)	0.3 (2)	0.1 (1)	0.4 (13)	0.354
GB-BHS	1.8 (8)	1.4 (8)	1.4 (10)	1.1 (8)	2.5 (18)	1.6 (52)	0.28
E. faecalis	1.6 (7)	1.6 (9)	2.5 (18)	3.1 (22)	2.8 (20)	2.4 (76)	0.31
E. faecium	2.0 (9)	1.8 (10)	3.4 (25)	3.0 (21)	5.4 (39)	3.3 (104)	**0.002**
E. coli	32.7 (145)	34.9 (197)	30.4 (222)	30.0 (213)	32.4 (233)	31.9 (1,010)	0.346
K. pneumoniae	10.8 (48)	12.4 (70)	13.0 (91)	12.4 (88)	12.4 (89)	12.3 (390)	0.867
Enterobacter	3.6 (16)	3.7 (21)	5.8 (42)	4.1 (29)	3.6 (26)	4.2 (134)	0.223
Serratia spp.	1.4 (6)	0.7 (4)	1.0 (7)	1.4 (10)	1.4 (10)	1.2 (37)	0.717
Proteus spp.	0.7 (3)	1.6 (9)	0.3 (2)	0.6 (4)	0.4 (3)	0.7 (21)	**0.043**
Salmonella spp.	1.1 (5)	1.2 (7)	0.8 (6)	0.3 (2)	0.6 (4)	0.8 (24)	0.275
A. baumannii	4.5 (20)	3.2 (18)	1.2 (9)	4.0 (28)	2.4 (17)	2.9 (92)	**0.005**
P. aeruginosa	5.0 (22)	2.5 (14)	3.4 (25)	3.8 (27)	3.2 (23)	3.5 (111)	0.296
S. maltophilia	0.0 (0)	0.5 (3)	0.5 (4)	1.0 (7)	0.8 (6)	0.6 (20)	0.3
C. albicans	1.8 (8)	2.1 (12)	3.7 (27)	2.9 (28)	3.3 (24)	3.1 (99)	0.142

Abbreviations: AHS, α-hemolytic streptococci; GA-BHS, group A β-hemolytic streptococci; GB, group B; *S. maltophilia*, *Stenotrophomonas maltophilia*

in regional variation or time differences. In the present study, positive blood culture decreased as time went on, which was inverse to blood culture rate.

Gram-positive bacteria caused 61.3% of BSI and 34.7% of BSI was caused by gram-negative bacteria. Among gram-positive bacteria, CoNS were the most common blood isolates (32.9%), which may be contaminated isolates, mostly. In addition, CoNS also were increasing agents to cause central line-associated BSI in immunocompromised patients. Therefore, the interpretation of blood cultures that are positive for CoNS is often difficult. The interpretation of blood culture that is positive for CoNS has inherent difficulties and requires careful reasoning (Tokars 2004). Except for CoNS, *E. coli*, *S. aureus*, *K. pneumoniae*, α-hemolytic streptococci, *Enterococcus* spp., *Enterobacter* spp., *P. aeruginosa*, *A. baumannii*, *Candida albicans*, and *S. pneumoniae* were the ten most common pathogens causing BSI in this study. Over period of ten years, *E. faecium* significantly increased but *S. pneumoniae*, *A. baumannii* and *Proteus* spp. decreased (Table 2). In addition, Koh et al. (2007) and Kim et al. (2012) reported increase of *E. faecium* from blood (3.6% to 10.1%, and 1.6% to 4.2%, respectively).

Although vancomycin could be usually used in the treatment of MRSA bacteremia, the mortality from MRSA bacteremia is higher than that from MSSA bacteremia, which may be due to the poor performance of vancomycin compared with penicillin used in MSSA. Therefore, accurate and rapid detection of MRSA in BSI is very important. In this study, overall incidence of MRSA was 60.8%, higher than that in 12 Asia-Pacific nations (37%) (Mendes et al., 2013), Latin America (48%) (Jones et al., 2013), European nations (31%) (Jones et al., 2014). During the study period, a significant increase of incidence of MRSA was observed (from 47.2% in 2003-2004 to 67.1% in 2011-2012) (Fig. 1). VRSA was not noted. VRSA has not been reported in the Republic of Korea yet but the isolates with higher vancomycin MIC increased, which showed the possibility

Table 3. Trends of antimicrobial resistance of common blood isolates over ten years

Microorganisms	Number of resistant isolates/total isolates tested within the years (percentage of resistant isolates)					
	2003-4	2005-6	2007-8	2009-10	2011-12	*P*-value
SAU						
CIP	28/72 (38.9)	37/96 (38.5)	51/138 (40.0)	69/153 (45.1)	62/131 (47.3)	0.364
OXA	34/72 (47.2)	50/96 (52.1)	84/138 (60.9)	103/153 (67.3)	88/131 (67.2)	**0.009**
PEN	65/72 (90.3)	89/96 (92.7)	132/138 (95.7)	150/153 (98.0)	122/131 (93.1)	0.104
TET	31/72 (43.1)	40/96 (41.7)	50/138 (36.2)	71/152 (46.4)	62/131 (47.3)	0.358
VAN	0/72 (0)	0/96 (0)	0/138 (0)	0/152 (0)	0/131 (0)	NA
EFA						
AMP	0/8 (0)	0/12 (0)	2/33 (6.1)	2/40 (5.0)	NA	0.754
VAN	0/8 (0)	0/12 (0)	1/33 (3)	2/40 (5)	0/24 (0)	0.711
EFM						
AMP	9/10 (90)	10/15 (66.7)	34/41 (82.9)	43/50 (86.0)	41/47 (87.3)	0.382
VAN	1/10 (10)	5/15 (33.3)	6/41 (14.6)	20/50 (40.0)	11/47 (23.4)	**0.047**
ECO						
AMP	92/157 (58.6)	108/215 (50.2)	141/262 (53.8)	163/260 (62.7)	157/244 (64.5)	**0.009**
AMK	4/157 (2.5)	4/215 (1.9)	2/262 (0.8)	3/260 (1.2)	3/244 (1.2)	0.60
CIP	32/157 (20.4)	44/215 (20.4)	64/262 (24.4)	40/260 (17.7)	28/244 (11.3)	**0.002**
CTX	10/157 (6.4)	14/215 (6.5)	40/262 (15.2)	46/260 (17.7)	64/244 (26.1)	**<0.001**
CZ	16/157 (10.2)	26/215 (12.0)	52/262 (19.8)	100/260 (38.5)	116/244 (47.7)	**<0.001**
KPN						
AMK	5/57 (8.8)	3/79 (3.8)	9/118 (7.6)	6/105 (5.7)	9/102 (8.8)	0.664
CIP	5/57 (8.8)	8/79 (10.1)	9/118 (7.6)	4/105 (3.8)	2/102 (2.0)	0.113
CTX	4/57 (7.2)	7/79 (8.9)	13/118 (11.1)	17/105 (16.1)	14/102 (13.7)	0.375
CZ	9/57 (15.8)	9/79 (11.4)	18/118 (15.2)	18/105 (17.1)	18/102 (17.7)	0.811
PAE						
CAZ	9/25 (36)	5/19 (26.3)	24/52 (46.2)	26/55 (47.3)	5/25 (20)	0.097
CIP	12/25 (48.0)	7/19 (36.8)	26/52 (50)	40/55 (72.7)	4/25 (16)	**<0.001**
IMP	4/25 (16.0)	8/19 (42)	17/52 (32.7)	31/55 (56.4)	5/25 (20)	**0.002**
ABA						
CAZ	13/21 (61.9)	6/18 (33.4)	5/11 (45.4)	20/27 (73.0)	15/19 (79.0)	**0.022**
CIP	7/21 (33.3)	5/18 (27.8)	5.11 (45.4)	20/27 (73.0)	11/19 (57.9)	**0.013**
IMP	3/21 (14.3)	0/18 (0)	3/11 (27.3)	12/27 (43.3)	11/19 (57.9)	**0.001**

Abbreviations: SAU, *Staphylococcus aureus*; CIP, ciprofloxacin; OXA, oxacillin; PEN, penicillin; TET, tetracycline; VAN, vancomycin; EFA, *Enterococcus faecalis*; AMP, ampicillin; EFM, *Enterococcus faecium*; ECO, *Escherichia coli*; AMK, amikacin; CTX, cefotaxime; CZ, cefazolin; KPN, *Klebsiella pneumoniae*; PAE, *Pseudomonas aeruginosa*; CAZ, ceftazidime; IMP, imipenem; ABA, *Acinetobacter baumannii* ; NA, not available.

of occurrence of VRSA in the Republic of Korea (Chung et al., 2010; Kim, 2011).

For treatment of serious enterococcal infection such as bacteremia, ampicillin and aminoglycosides are the drugs of choice. Diseases caused by strains resistant to ampicillin and aminoglycosides can be treated with vancomycin. In this study, ampicillin resistance in *E. faecalis* and *E. faecium* were 11.1% and 85.3%, respectively. In addition, Koh et al.

(2007) and Kim et al. (2012) reported that the resistant rates of *E. faecium* to ampicillin in blood isolates had been raised to 90% and 88.6%, respectively. These findings are similar to other studies (Koh et al., 2007; Kim et al., 2012). In addition, vancomycin resistance in these bacteria was 2.6% and 26.4%, respectively. Vancomycin resistance in *E. faecium* increased from 10% in 2003-2004 to 23.4% in 2011-2012. The occurrence of VRE represents a serious problem because the treatment of infections provoked by VRE may be highly problematic as the choice of suitable medicaments is limited mostly to linezolid and quinupristin/dalfopristin, or because of the transmission of vancomycin resistant genes, such as *van*A or *van*B etc. A significant correlation between vancomycin use and VRE occurrence was proved (Quale et al., 1996; Empey and Rapp, 2002; Kolar et al., 2002) and use of infection control measures including hand hygiene, has been successful in containing small monoclonal outbreaks (Boyce et al., 1994). Therefore, the VRE problem requires not only improved hygiene in the department but also responsible use of antibiotics.

In *E. coli*, the most common cause of bacteremia except CoNS, the resistance rate for first generation, third generation cephalosporin and aztreonam increased over a period of time. However, a significant change was not shown in that of *K. pneumoniae*, the second cause of bacteremia in Enterobacteriaceae. ESBL producing *E. coli* is an emerging cause of nosocomial healthcare-associated, and community-acquired infection worldwide (Jacobby and Medeiros, 1991; Bush, 2001). Inadequate empirical antibiotic therapy for infections caused by this microorganism is associated with poor outcomes, especially in bacteremia, and the use of carbapenem or cefepime is only effective for patients with bacteremia by ESBL (Ramphal and Ambrose, 2006). In addition, resistant isolates for imipenem were not observed in this study. However, recently isolates producing carbapenemase, such as NDM, KPC (Nordmann et al., 2011; Kim et al., 2013), have been reported worldwide. Therefore more constricted surveillance must be required in the clinical laboratory.

Recently, an increase of IRAB and IRPA has become serious problem. In this study, IRAB during 2003-2006 was 7.7% but abruptly increased to 37.5% in 2007 and to 44.7% during 2007-2012, which was similar to other studies in the Republic of Korea (Lee et al., 2009; Lee et al., 2011; Kim et al., 2012). In addition, IRPA in 2003 increased to 59% in 2009 and increased to 45% during 2009-2012. OXA-type carbapenemase, IMP and VIM type imipenemase producing isolates may be major causes of imipenem resistance in this isolates (Shin et al., 2008; Lee et al., 2009; Jeong et al., 2011). Therefore, rapid detection or strict control of transmission of these isolates producing carbapenemase must be required.

This study has several limitations due to the fact that it was a retrospective study. First, the results of antimicrobial susceptibilities testing obtained from conventional disk diffusion or the Vitek II system were confirmed by the E-test only in isolates with vancomycin- or imipenem-resistance. Second, we did not conduct the interpretation of the positive cultures in term of contamination or clinically relevant infection. Third, we did not perform epidemiologic studies to identify clonally relatedness, such as pulsed-field gel electrophoresis (PFGE).

In conclusion, *E. coli* was the most frequent etiologic agent of bacteremia except CoNS, and *S. aureus*, *K. pneumoniae* and α-hemolytic *Streptococcus* were frequently isolated pathogens over ten years in a university hospital. In addition, multidrug-resistant microorganisms, such as MRSA, VRE, CTX-resistant *E. coli*, IRPA and IRAB gradually increased, which requires stricter control of antibiotics and the need for a more updated guideline for the treatment of bloodstream infections.

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