

## A 6-YEAR RETROSPECTIVE ANALYSIS ON THE SPECIES DISTRIBUTION AND ANTIMICROBIAL SUSCEPTIBILITY OF PATHOGENS IN BLOOD CULTURES

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### ABSTRACT

It is important for microbiological workers to perform periodic surveillances on the emergence of isolates from positive blood cultures and their antibiotic resistance. The aim of this study is to evaluate the common pathogenic distribution and antimicrobial susceptibility of pathogens isolated from aerobic and anaerobic bottles for the past six years. From January 2010 to December 2015, 9122 bottles were tested using an automated blood culture detection system. From 9122 bottles, 745 positive bottles yielded 450 organisms. Of these, 250 (55.6%) were Gram-negative bacteria, 184 (40.9%) were Gram-positive bacteria and 16 (3.6%) were fungi. *Escherichia coli* and *Staphylococcus* spp were the most frequently isolated species for Gram-negative and Gram-positive bacteria, respectively. Amikacin, meropenem, imipenem, vancomycin, linezolid and quinupristin-dalfopristin may be the best choices to use for positive blood cultures in the hospital. The periodic surveillance of the common pathogenic distribution isolated from bottles and their antimicrobial susceptibilities can help medical workers to recognize the emergence and rapid dissemination of pathogens with high rates of resistance to most commonly used antibiotics.

**Key Words:** Blood culture; Species distribution; Antimicrobial susceptibility.

### INTRODUCTION

Bacterial bloodstream infections can lead to the high morbidity and mortality of people globally. Thus, it is important for laboratories to detect pathogens on time and identify these pathogens using an optimal blood culture system and technology to initiate the right antimicrobial therapy. Accurate and timely blood culture results are essential for medical workers to provide appropriate antibiotic therapy for patients with sepsis or septicemia [1]. Most medical institutions rely on an automated blood culture system to detect blood pathogens. In our hospital, no studies have analyzed the distribution of pathogens and the antimicrobial susceptibility of these pathogens from commercially available BACTEC blood bottles. Therefore, we conducted this study.

### Materials and methods

A retrospective study was conducted in the Department of Clinical Laboratory. Data analysis was carried out between January 2010 and December 2015. A total of 745 positive blood culture samples were examined by our lab.

The culture bottles were incubated using the BACTEC 9240 blood culture system. A blood culture set (consisting of one resin-containing BACTEC Plus

Aerobic/F and one BACTEC Lytic/10 Anaerobic/F) were incubated at 35°C with continuous rocking agitation for 5 days, and tested by the system unit every ten minutes. The bottles were discarded if no microbial growth was detected by the fluorescence technology system (over 5 days). The parts of the bottles flagged as positive were used for Gram staining and subcultured on blood agar plates and China blue agar plates for further identification. Bacterial identification and antimicrobial susceptibility of the isolated pathogens were performed using the BD phoenix Automated Microbiology System.

Each bloodstream infection was defined as the isolation of a unique organism from one, two, or more bottles collected within 7 days along with clinical evidence of infection, the repeated isolation of the same pathogen after 7 days of the last known positive culture, or a pathogen which was different from the initial pathogen. If more than two culture bottles from the same patient were positive, only one bottle was used for the antimicrobial susceptibility assay. Reference strains of *Escherichia Coli* (ATCC 25922), *Pseudomonas aeruginosa* (ATCC 27853), *Enterococcus faecalis* (ATCC 29212) and *Staphylococcus aureus* (ATCC 29213) were used as quality control strains according to the manufacturer's instructions. Additional tests were conducted if the yielded results of the BD Phoenix Automated Microbiology System had <90% confidence.

### RESULTS

During the study period, a total of 9122 blood

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bottles were submitted to the lab, and 745 (8.2%) positive bottles (445 aerobic bottles and 300 anaerobic bottles) yielded 450 organisms in this study. Of the patients (n = 426) with positive blood cultures, 168 (39.4%) were females and 258 (60.6%) were males, with a mean age of 69.8 years (range 19–99 years). Among the 450 isolates, 402 isolates (89.3%) were single species. Of the 450 isolates, 250 (55.6%) were Gram-negative bacteria, 184 (40.9%) were Gram-positive bacteria and 16 (3.6%) were fungi. The ten most common isolates accounted for 351 (78%) of all the isolates. Of these, 155 isolates from bottles ( $\geq 1$  set blood culture) were analyzed, and 137 were detected in the aerobic bottles only and 59 were from anaerobic bottles only.

As shown in Table 1, *Escherichia Coli* was the predominant Gram-negative bacteria followed by *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and *Enterobacter cloacae*. The five leading pathogens classified as Gram-positive bacteria were *Staphylococcus epidermidis*, *Staphylococcus aureus*, *Enterococcus faecalis*, *Enterococcus faecium*, and *Staphylococcus haemolyticus*. All isolates of *A. baumannii* were observed in aerobic bottles. For those positive bottles with *P. aeruginosa* and *S. haemolyticus* isolates, only a few isolates grew in anaerobic bottles compared to that of aerobic bottles, and no isolates of *P. aeruginosa* and *S. haemolyticus* grew only in anaerobic bottles. Furthermore, compared to *E. faecium*, the isolates of *E. faecalis* grew more in anaerobic bottles. Almost all the isolates of *C. albicans* were observed in the aerobic bottles, and only one isolate grew in an anaerobic bottle (data not shown). We also found that nine isolates were obligate anaerobes (eight Gram-negative and one Gram-positive). Table 2 and Table 3 show the

antimicrobial susceptibility test results performed during the study period. Higher amikacin, meropenem and imipenem susceptibilities were found of more than 77.1%, 61.5% and 69.2% respectively among the four Gram-negative bacteria isolates tested except for *A. baumannii* isolates. Only aztreonam displayed the highest susceptibility (54.2%) for *A. baumannii*. Vancomycin, linezolid and quinupristin/dalfopristin susceptibility remained high (79.8%, 84.2% and 89.5%) for the five leading pathogens in Gram-positive bacteria respectively, and no resistance were found to vancomycin and linezolid among the three *Staphylococcus* spp.

## DISCUSSION

The blood culture system has improved the ability to continuously monitor positive bottles as soon as possible, including the addition of various bottles type, advances in the agitation system, and the development of related software. The rapid detection and identification of pathogens from blood culture bottles is important for lab workers. At the same time, empirical antimicrobial therapy has been shown to have the greatest impact on patients outcomes, so we need to provide information on the common pathogenenic distribution and antimicrobial susceptibility in a timely manner. In our study, a retrospective survey was conducted on 745 positive blood culture samples from the microbiology lab between January 2010 and December 2015. In this study, a blood culture set consists of one resin-containing BACTEC Plus Aerobic/F bottle and one BACTEC Lytic/10 Anaerobic/F bottle. The BACTEC Aerobic Plus resin bottle contains resin which bind and neutralize a wide variety of antimicrobial agents, although it may occasionally not do well for some antibiotics [2]. The

**Table1. Top of 10 pathogens detected in BACTEC blood culture bottles. (2010.1.1 – 2015.12.31)**

Pathogen	No. of isolates	Growth in aerobic bottles only	Growth in anaerobic bottles only	Growth in both bottles ( $\geq 1$ culture)	No. of positive bottles	Growth in aerobic bottles	Growth in anaerobic bottles
<i>E.coli</i>	95 (44.2%)	25	21	49	158	82	76
<i>K. pneumoniae</i>	48 (22.3%)	14	8	26	98	50	48
<i>P. aeruginosa</i>	31 (14.4)	24	0	7	39	31	8
<i>A. baumannii</i>	28 (13%)	28	0	0	37	37	0
<i>E. cloacae</i>	13 (6%)	4	1	8	24	14	10
Total	215	95 (44.2%)	30 (14%)	90 (41.9%)	356	214 (60.1%)	142 (39.9%)
<i>S. epidermidis</i>	47 (34.6%)	14	9	24	75	40	35
<i>E. faecalis</i>	26 (19.1%)	1	10	15	61	26	35
<i>S. aureus</i>	25 (18.4%)	7	8	10	40	21	19
<i>E. faecium</i>	19 (14%)	7	2	10	36	20	16
<i>S. haemolyticus</i>	19 (14%)	13	0	6	25	19	6
Total	136	42 (30.9%)	29 (21.3%)	65 (47.8%)	237	126 (53.2%)	111 (46.8%)

**Table 2. Antimicrobial susceptibility pattern of the top five Gram negative bacterial isolates from blood culture.**

	E.coli(N=95)	K. pneumoniae (N=48)	P. aeruginosa (N=31)	A. baumannii (N=28)	E. cloacae (N=13)
AN	93.7%	77.1%	100%	25%	84.6%
AMC	41%	47.9%	0	0	0
AM	9.5%	0	0	0	0
ATM	42.1%	54.2%	61.3%	53.6%	38.5%
CIP	26.3%	58.3%	87.1%	14.3%	53.8%
MEM	98.9%	79.2%	90.3%	25%	61.5%
PIP	12.6%	33.3%	77.4%	0	30.8%
TZP	85.3%	50%	87.1%	14.3%	46.2%
GM	47.4%	58.3%	90.3%	17.9%	46.2%
TE	28.4%	60.4%	0	21.4%	53.8%
FEP	42.1%	54.2%	64.5%	10.7%	61.5%
CTX	35.8%	52.1%	0	3.6%	38.5%
CAZ	50.5%	56.3%	71%	17.9%	46.2%
IPM	97.9%	79.2%	77.4%	25%	69.2%
LVX	28.4%	66.7%	77.4%	17.9%	53.8%

AN, Amikacin; AMC, Amoxicillin/Clavulanate; AM, Ampicillin; ATM, Aztreonam; CIP, Ciprofloxacin; MEM, Meropenem; PIP, Piperacillin; TZP, Piperacillin/Tazobactam; GM, Gentamicin; TE, Tetracycline; FEP, Cefepime; CTX, Cefotaxime; CAZ, Ceftazidime; IPM, Imipenem; LVX, Levofloxacin.

BACTEC Lytic/10 Anaerobic/F bottle could destroy red blood cells, white blood cells and platelets, while at the same time release bacteria from circulating macrophages, increase positive detection rate, and shorten the reporting time. For some strains, the recovery was faster from anaerobic lytic bottles than aerobic resin-containing bottles [3]. Paired culture sets are recommended according to the Clinical and Laboratory Standards Institute guidelines [2].

In our study, a total of 745 positive bottles were identified which included 445 aerobic bottles and 300 anaerobic bottles. Almost all the isolates of *A. baumannii*, *P. aeruginosa*, *S. haemolyticus*, *C. albicans*, *B. cepacia*, *S. maltophilia*, *O. anthropi*, and *Cedecea. spp* were detected only in aerobic bottles. It was not surprising that these bottles with detected growth contained aerobic medium because that they are generally obligate aerobes. The isolates of *S. lugdunensis*, *S. equorum*, *S. sciuri*, *S. constellatus*, *S. oralis*, and *S. pasteuri* were detected only in anaerobic bottles. Despite a few uncommon strains in our data, such as one *S. maltophilia*, other studies have shown that its mortality rate was high as a marker of serious pathology [4]. In addition, it was noteworthy that in this study there were 24 cases where more than one pathogen was isolated from one or more blood culture bottles.

As shown in Table 1, the ratio of Gram-negative isolates to Gram-positive isolates was about 1.6:1. *E. coli* (44.2%), and *K. pneumoniae* (22.3%) were the

more frequently isolated species for Gram-negative bacteria. This finding supports the results observed by other studies [5-6]. In addition, *S. epidermidis* (34.9%) was the most frequently isolated species for Gram-positive bacteria. This finding supports the prior observation that *S. epidermidis* was the leading pathogen in early-onset sepsis [6]. All patients with isolates of coagulase-negative *Staphylococcus* should be evaluated by physicians to determine whether or not their real bloodstream was infected [7]. Our results had a higher proportion of *Staphylococcus aureus* among the Gram-positive bacteria. This bacteria is a common and most lethal cause of blood stream infections [8].

It was also interesting to find that the number of aerobic bottles was larger than that of the anaerobic bottles for the ten most common bacteria, except for *E. faecalis*. This indicates the unique characteristics of blood culture for *E. faecalis*. High numbers of facultative anaerobes were detected in the anaerobic and aerobic bottles. Using both bottles might have an important effect on the clinical therapy outcome [9].

Table 2 shows that there was higher amikacin, meropenem and imipenem susceptibility among the four Gram-negative bacteria isolates tested except for *A. baumannii* isolates. We found that there was a 100% susceptibility of amikacin for *P. aeruginosa*. The *A. baumannii* isolates showed high resistance for most antibiotics, and only aztreonam displayed the

**Table 3. Antimicrobial susceptibility pattern of the top five Gram Positive bacterial isolates from blood culture.**

	<b>S. epidermidis (N=47)</b>	<b>E. faecalis (N=26)</b>	<b>S. aureus (N=25)</b>	<b>E. faecium (N=19)</b>	<b>S. haemolyticus (N=19)</b>
AM	0	88.5%	0	0	0
GMX	NA	38.5%	NA	47.4%	NA
LZD	100%	88.5%	100%	84.2%	100%
VA	100%	92.3%	100%	78.9%	100%
CIP	31.9%	NA	48%	NA	10.5%
E	23.4%	NA	24%	NA	5.3%
GM	36.2%	NA	40%	NA	15.8%
OX	6.4%	NA	40%	NA	10.5%
P	0	NA	0	NA	0
RA	87.2%	NA	56%	NA	89.5%
SXT	29.8%	NA	76%	NA	57.9%
SYN	85.1%	NA	96%	NA	89.5%
TE	68.1%	NA	44%	NA	73.7%

AM, Ampicillin; GMX, Gentamicin-syn; LZD, Linezolid; VA, Vancomycin; CIP, Ciprofloxacin; E, Erythromycin; GM, Gentamicin; OX, Oxacillin; P, Penicillin; RA, Rifampin; SXT, Trimethoprim/Sulfamethoxazole; SYN, Quinupristin/Dalfopristin; TE, Tetracycline; NA, not applicable.

highest susceptibility (54.2%).

As shown in Table 3, there were higher susceptibilities towards vancomycin, linezolid, quinupristin/dalfopristin and lower susceptibility towards penicillin among the three *Staphylococcus* spp. In addition, the two *Enterococcus* spp had higher susceptibilities towards vancomycin and linezolid. Nevertheless, it was noteworthy to compare the rates of ampicillin susceptibilities for *E. faecalis* and the other four most common Gram-positive isolates (88.5% vs. 0%) in our findings. The main findings of the present study was that vancomycin, linezolid, and quinupristin/dalfopristin were effective for Gram-positive bacteria, while amikacin, meropenem and imipenem were effective for Gram-negative bacteria. The antibody susceptibility pattern of isolates were different from the results reported by other studies [10]. Therefore, the *in vitro* susceptibility of this study highlights that these six antibiotics would be effective for the treatment of bloodstream infections in this area.

There are several potential limitations of this study. Information about the early availability of microbiological information (such as Gram stain findings, time of detection and so on) should be discussed briefly, which would be of enormous value in improving the outcome of severely infected patients. This is because timeliness and accuracy of preliminary blood culture reports are core laboratory quality performance indicators in the practice of assessing blood cultures [11].

Another limitation in our study which has to be

pointed out is the incubation time for the *Candida* species. Although the *Candida* species rank lower among the pathogens isolated from the blood cultures in our study and little information was gained, we must consider the question of whether we should prolong the incubation time, perform terminal subcultures, or utilize specific mycology blood bottles for the detection of certain pathogens when using the BACTEC 9240 system. This is because we noted that for *C. glabrata*, the time to detection with the automated blood culture system was significantly longer in the aerobic medium than in the anaerobic medium, and was also longer than for other *Candida* spp. in aerobic mediums [12]. Compared to *C. albicans*, *C. parapsilosis*, *C. tropicalis* and *C. krusei*, a time-to-positivity of  $\leq 56.5$  h, growth only or earlier in aerobic bottles would be useful to rule out *C. glabrata* for early treatment optimization as reported by other studies [13]. Despite these shortcomings, our data are critically important and could perhaps facilitate physicians to perform the initiation of appropriate empiric antibiotic treatment to some degree.

In conclusion, loading culture bottles into the instrument promptly is recommended in the microbiology laboratories of most hospitals. Good lab facilities, optimal testing parameters, phlebotomy team strategies or sterile collection kits are necessary to help medical workers have good guidelines for antibiotic use, during the empirical, early, or late periods [14-16]. Blood cultures remain a reliable and most practical method in the diagnosis of bloodstream infection, but other accurate and

cost-effective methods are also used in clinical microbiology lab for rapid identification. One example is matrix-assisted laser desorption ionization-time of flight mass spectrometry, used especially for the rapid identification of Gram-negative Bacilli from blood cultures to influence the selection of the right antimicrobial therapy [17-18]. Although less of a gold standard regular diagnostic procedure, the PCR method could be valuable when used complementarily for bone marrow transplants with bloodstream infections [19]. In addition, peptide nucleic acid fluorescent in situ hybridization (PNA-FISH) is also a possible method for the detection of species directly from positive blood culture bottles and peritoneal fluid cultures, in spite of a requirement to have more than  $10^5$  CFU/mL for detected organisms [20].

It is important for those in clinical medicine to perform blood cultures to detect pathogens and guide antibiotic therapy.<sup>21</sup> Lab workers would have to consider adjusting the protocols accordingly because of several potential problems, including the timing of collection and loading the bottles into the instrument, type of culture bottle, longer time to detection with small inoculum sizes, and unusual growth characteristics of some pathogens, one shift per microbiology laboratory, the prior use of antibiotics, best practices (venipuncture and the use of phlebotomy teams), and repeat blood culture despite an initial negative blood culture with febrile neutropenia patients [1,2,9,12,22-24]. So it is important for both lab workers and physicians to understand the advantage, limitations and possible solutions for various automated blood culture system technologies, and perform oral-alert or written reports with good clinical advice [16,25]. The physician could request longer durations when clinically indicated.

With an increasing incidence of blood pathogens (including *Candida* species isolates), lab workers should also consider prolonging the incubation time of the blood culture, performing terminal subcultures before discarding, or using specific media for some pathogens based on the actual situation. Our study highlights that it is important for microbiological workers to perform periodic surveillances on the emergence of isolates from positive blood cultures and their antibiotic resistance.

## ACKNOWLEDGEMENTS

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