Analysis of community- and hospital-acquired bacteraemia during a recent 5-year period

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There are sparse data concerning sex- and age-specific characteristics of community-acquired bacteraemia (CAB) and hospital-acquired bacteraemia (HAB). Between January 2008 and December 2012, we identified 2956 bacteraemia cases, which we classified as CAB, HAB or healthcare-associated bacteraemia (HCAB). Almost half of the pathogens were Escherichia coli in CAB patients. By contrast, Staphylococcus aureus was most frequent (16.2 %) in HAB patients. HCAB showed mixed features of CAB and HAB. In CAB, E. coli was significantly more abundant in females than in males (56.9 vs 24.3 %, respectively). This trend was most striking in young adults (20–39 years) (77.2 % in females vs 11.4 % in males). HAB cases showed greater heterogeneity in their associated pathogens. The extended-spectrum β-lactamase-positive rates of E. coli and Klebsiella pneumoniae, respectively, were 31.3 and 33.8 % in HAB and 8.8 and 8.4 % in CAB. The non-susceptibility rates of S. aureus to oxacillin were 37.4 % in CAB and 73.0 % in HAB. In conclusion, CAB and HAB showed different distributions of micro-organisms, and these distributions also differed with patient age and sex. In addition, antimicrobial susceptibility needs to be monitored separately.

INTRODUCTION

Although blood culture techniques have improved and have provided reliable results that inform about treatment options (Cockerill et al., 2004), some patients need immediate empiric treatment before obtaining blood culture results. A better understanding of the distribution of micro-organisms in bacteraemic blood cultures can inform about this empiric treatment. The trends in microbial isolates from bacteraemic blood cultures, however, have changed through the decades due to changes in host-associated factors such as the use of prosthetic devices and organ transplantation, as well as through the improvement of blood culture techniques (Weinstein et al., 1997). Moreover, dominant micro-organisms in bacteraemia vary greatly according to geographical location, age and sex of patients, and type of bacteraemia.

We also expect that community-acquired bacteraemia (CAB) and hospital-acquired bacteraemia (HAB) have different distributions of associated micro-organisms and different antimicrobial susceptibilities. A comprehensive analysis of the micro-organisms associated with each type of bacteraemia, the antimicrobial susceptibilities of these pathogens, and how these factors differ with patient age and sex could help guide empiric treatment policies. Although there have been several studies concerning bacteraemia-positive blood cultures in South Korea, most studies did not distinguish between CAB and HAB (Kim et al., 2011; Huh et al., 2013). Moreover, to the best of our knowledge, there are sparse data on sex- and age-specific characteristics of CAB and HAB worldwide.

To better understand bacteraemia and potentially improve guidelines for empiric treatment of patients, we evaluated the sex- and age-specific microbial characteristics of CAB and HAB from 2008 to 2012 in South Korea. In addition, we assessed the antimicrobial susceptibilities of common pathogens isolated from patients with CAB and HAB.

METHODS

Study design. From January 2008 to December 2012, we conducted a retrospective study using data from laboratory and hospital databases collected at a tertiary university hospital with ~900 beds in Seoul, South Korea. A total of 12 324 bacteraemia-positive test results were collected. After excluding duplicated entries from the same patient and potential false-positive, contaminated test results, we identified 2956 cases of bacteraemia. The study protocol was approved by the institutional review boards of Konkuk University Medical Center.
**Definitions.** Bacteraemia was classified as CAB, HAB or healthcare-associated bacteraemia (HCAB). CAB was defined as bacteraemia in patients who had pathogenic micro-organisms isolated from blood within the first 2 days of hospitalization and without a hospital stay in the 30 days prior to admission. HAB was defined as bacteraemia in patients who had pathogenic micro-organisms isolated from blood cultures taken ≥2 days after admission. Finally, HCAB was defined as bacteraemia in patients who had pathogenic micro-organisms isolated from blood within the first 2 days after admission but who had a hospital stay within 30 days of the admission (Siegman-Igra et al., 2002; Kanoksil et al., 2013). Micro-organisms that were generally considered to be contaminants, including *Corynebacterium* spp., *Bacillus* spp., *Micrococcus* spp., and *Propionibacterium* spp., were excluded from the analysis. In this study, coagulase-negative staphylococci (CoNS) were excluded in the main analysis because the number of blood culture sets was variable and it was difficult to define clinical significance. However, we included CoNS in the analysis of antimicrobial susceptibility. When more than one pathogen was isolated from a single blood culture (polymicrobial bacteraemia), each pathogen was analysed separately (Cockerill et al., 2004).

**Blood culture.** During the study period, a minimum of 20 ml blood (1–5 ml in children) was recommended for blood culture. Blood culture was performed using the BacT/Alert system (bioMérieux). Broths from positive cultures were Gram stained and subcultured. Bacterial identification and antimicrobial susceptibility testing were performed using the VITEK 2 system (bioMérieux). All microbiological methods were consistent with the current Clinical and Laboratory Standards Institute (CLSI) guidelines and antimicrobial susceptibility was determined using the CLSI breakpoints (CLSI, 2011).

**Statistical analysis.** The χ² test or Fisher’s exact test was used for categorical variables, and Student’s t-test was used for continuous variables, as appropriate. Statistical analysis was performed using SPSS software (version 14.0) and MedCalc statistical software (version 11.2.1). P<0.01 was considered to be statistically significant.

**RESULTS**

**Characteristics of CAB, HAB and HCAB**

Among 2956 cases of bacteraemia, 1423 were classified as CAB, 1322 as HAB and 211 as HCAB. This distribution differed significantly according to patient sex (P<0.001 by χ² test). Female patients were more frequently diagnosed with CAB (male, 43.9 %), whereas males were more frequently affected by HAB (male, 53.0 %) and HCAB (male, 58.3 %). The mean ages were not significantly different between CAB, HAB and HCAB (61.4, 59.9 and 58.3 years old, respectively).

Almost half of the CAB cases were associated with *Escherichia coli* (42.6 %) infection, followed by *Klebsiella pneumoniae* (14.1 %), *Streptococcus* spp. (12.3 %), *Staphylococcus aureus* (10.6 %), *Enterococcus* spp. (3.0 %) and *Enterobacter* spp. (1.9 %). In HAB, *S. aureus* (16.2 %) was the most frequent pathogen, followed by *Enterococcus* spp. (15.8 %), *E. coli* (14.7 %), *Candida* spp. (12.9 %), *K. pneumoniae* (12.5 %) and *Pseudomonas aeruginosa* (5.4 %). HCAB showed mixed features of CAB and HAB. Similar to CAB, the most frequent HCAB pathogens were *E. coli* (36.5 %) and *Streptococcus* spp. (8 %). However, *P. aeruginosa*, which was common in HAB patients but rarely associated with CAB, was frequent (4.7 %) in HCAB patients (Table 1).

**Sex- and age-specific distributions of CAB pathogens**

The distribution of pathogens was significantly different in males and females. *E. coli* was the most frequent CAB-associated pathogen in both males and females; however, it was significantly more abundant in females than in males (56.9 vs 24.3 %, respectively; P<0.001 by χ² test). This trend was most striking in young adults (20–39 years) (77.2 % in females vs 11.4 % in males). *Streptococcus* spp. were the most frequent pathogens in children and adolescents, and group B *Streptococcus* was observed exclusively in infants (<1 year) and in the advanced-aged group (≥60 years). *P. aeruginosa*, *Acinetobacter baumannii*, *Candida* spp. and *Salmonella* spp. were rarely observed in CAB (Table 2).

**Sex- and age-specific distributions of HAB pathogens**

Many heterogeneous pathogens were observed in HAB, and *S. aureus*, *Enterococcus* spp., *E. coli*, *Candida* spp., *K. pneumoniae* and glucose non-fermenting Gram-negative bacillus, including *P. aeruginosa* and *A. baumannii*, were observed frequently. The distributions of these microbes differed with sex and age. In infants, *S. aureus* and *Enterococcus* spp. were the predominant pathogens for both sexes (33.3 and 14.8 % in males; 30.4 and 34.8 % in females). *E. coli* and *Enterococcus* spp. were the most frequent pathogens in young male adults (20–39 years; 20.5 and 18.2 %, respectively). By contrast, *S. aureus* was more common (18.0 %) in young female adults in addition to *E. coli* and *Enterococcus* spp. (both pathogens, 16.0 %). In the middle-aged group (40–59 years), *K. pneumoniae* and *Enterococcus* spp. were more frequent in males (both pathogens, 17.5 %), and *S. aureus* and *E. coli* were more common in females (18.6 and 17.3 %, respectively). In the advanced-aged group (≥60 years), *Candida* spp. were more frequent in males (18.7 %) and *E. coli* was more frequent in females (21.4 %). The next most frequent pathogens were *S. aureus* and *Enterococcus* spp. in advanced-aged groups of both sexes (Table 2).

**Comparison of antimicrobial susceptibility of pathogens isolated from CAB and HAB**

The antimicrobial resistance of the major pathogens isolated from patients with CAB and HAB is shown in Table S1 (available in the online Supplementary Material). The extended-spectrum β-lactamase (ESBL)-positive rates of *E. coli* and *K. pneumoniae* were 31.3 and 33.8 % in HAB and 8.8 and 8.4 % in CAB, respectively. The non-susceptibility
rates for oxacillin among \textit{S. aureus} and CoNS were 37.4 and 56.6\% in CAB and 73.0 and 89.3\% in HAB. No vancomycin-, linezolid- or quinupristin–dalfopristin-resistant \textit{S. aureus} was present in CAB or HAB cases. Vancomycin-resistant \textit{Enterococcus} spp. occurred with a frequency of 5.3\% in CAB and 24.3\% in HAB.

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|}
\hline
\textbf{Rank} & \textbf{CAB (N=1423)} & \textbf{HAB (N=1322)} & \textbf{HCAB (N=211)} \\
\hline
1 & \textit{Escherichia coli} (42.6\%) & \textit{Staphylococcus aureus} (16.2\%) & \textit{Escherichia coli} (36.5\%) \\
2 & \textit{Klebsiella pneumoniae} (14.1\%) & \textit{Enterococcus} spp. (15.8\%) & \textit{Klebsiella pneumoniae} (15.6\%) \\
3 & \textit{Streptococcus} spp.* (12.3\%) & \textit{Escherichia coli} (14.7\%) & \textit{Staphylococcus aureus} (10.9\%) \\
4 & \textit{Staphylococcus aureus} (10.6\%) & \textit{Candida} spp. (12.9\%) & \textit{Streptococcus} spp.* (8.0\%) \\
5 & \textit{Enterococcus} spp. (3.0\%) & \textit{Klebsiella pneumoniae} (12.5\%) & \textit{Pseudomonas aeruginosa} (4.7\%) \\
6 & \textit{Enterobacter} spp. (1.9\%) & \textit{Pseudomonas aeruginosa} (5.4\%) & \textit{Enterococcus} spp. (5.2\%) \\
\hline
\end{tabular}
\caption{Rank order of organisms isolated from patients with CAB, HAB and HCAB}
\end{table}

*Including \textit{S. pneumoniae}, group A and B streptococci.

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|c|c|}
\hline
\textbf{Age group (years)} & \multicolumn{6}{|c|}{\textbf{Total}} \\
\cline{2-7}
\textbf{CAB} & \leq 19 & 20–39 & 40–59 & \geq 60 & \multicolumn{2}{|c|}{\textbf{Total}} \\
\hline
Male (N) & 34 & 35 & 198 & 358 & 625 & \\
\textit{E. coli} & 6 (17.6) & 4 (11.4) & 41 (20.7) & 101 (28.2) & 152 (24.3) & \\
\textit{K. pneumoniae} & 3 (8.8) & 7 (20.0) & 36 (18.2) & 70 (19.6) & 116 (18.6) & \\
GNFB & 1 (2.9) & 5 (14.3) & 14 (7.1) & 16 (4.5) & 36 (5.8) & \\
\textit{S. aureus} & 3 (8.8) & 7 (20.0) & 36 (18.2) & 46 (12.8) & 92 (14.7) & \\
\textit{Streptococcus} spp. & 13 (38.2) & 6 (16.6) & 36 (18.2) & 49 (13.7) & 104 (17.1) & \\
\textit{Enterococcus} spp. & 0 (0.0) & 0 (0.0) & 5 (2.5) & 18 (5.0) & 23 (3.7) & \\
\textit{Candida} spp. & 0 (0.0) & 0 (0.0) & 3 (1.5) & 11 (3.1) & 14 (2.2) & \\
Female (N) & 15 & 92 & 186 & 505 & 798 & \\
\textit{E. coli} & 5 (33.3) & 71 (77.2) & 112 (60.2) & 266 (52.7) & 454 (56.9) & \\
\textit{K. pneumoniae} & 0 (0.0) & 0 (0.0) & 17 (9.1) & 67 (13.3) & 84 (10.5) & \\
GNFB & 0 (0.0) & 2 (2.2) & 6 (3.2) & 11 (2.2) & 19 (2.4) & \\
\textit{S. aureus} & 3 (20.0) & 4 (4.3) & 9 (4.8) & 43 (8.5) & 59 (7.4) & \\
\textit{Streptococcus} spp. & 6 (40.0) & 4 (4.3) & 21 (11.3) & 33 (6.5) & 84 (8.0) & \\
\textit{Enterococcus} spp. & 0 (0.0) & 1 (1.1) & 4 (2.2) & 15 (3.0) & 20 (2.5) & \\
\textit{Candida} spp., non-\textit{albicans} & 0 (0.0) & 2 (2.2) & 3 (1.6) & 9 (1.8) & 14 (1.8) & \\
\hline
\textbf{HAB} & \multicolumn{6}{|c|}{\textbf{Total}} \\
\hline
Male (N) & 27 & 44 & 240 & 390 & 701 & \\
\textit{E. coli} & 0 (0.0) & 9 (20.5) & 27 (11.3) & 38 (9.7) & 74 (10.6) & \\
\textit{K. pneumoniae} & 4 (14.8) & 5 (11.4) & 42 (17.5) & 51 (13.1) & 102 (14.6) & \\
GNFB & 3 (11.1) & 8 (18.2) & 34 (14.2) & 57 (14.6) & 102 (14.6) & \\
\textit{S. aureus} & \textbf{9 (33.3)} & 3 (6.8) & 28 (11.7) & 62 (15.9) & 102 (14.6) & \\
\textit{Streptococcus} spp. & 0 (0.0) & 2 (4.5) & 11 (4.6) & 12 (3.1) & 25 (3.4) & \\
\textit{Enterococcus} spp. & 4 (14.8) & 8 (18.2) & \textbf{42 (17.5)} & 55 (14.1) & \textbf{109 (15.5)} & \\
\textit{Candida} spp. & 2 (7.4) & 3 (6.8) & 21 (8.8) & 73 (18.7) & 99 (14.1) & \\
Female (N) & 23 & 50 & 156 & 392 & 621 & \\
\textit{E. coli} & 2 (8.7) & 8 (16.0) & 27 (17.3) & \textbf{84 (21.4)} & \textbf{121 (19.5)} & \\
\textit{K. pneumoniae} & 2 (8.7) & 4 (8.0) & 19 (12.2) & 38 (9.7) & 63 (10.1) & \\
GNFB & 0 (0.0) & 5 (10.0) & 24 (15.4) & 53 (13.5) & 82 (13.2) & \\
\textit{S. aureus} & 7 (30.4) & \textbf{9 (18.0)} & \textbf{29 (18.6)} & 67 (17.1) & 112 (18.0) & \\
\textit{Streptococcus} spp. & 0 (0.0) & 5 (10.0) & 5 (3.2) & 5 (1.3) & 15 (2.4) & \\
\textit{Enterococcus} spp. & \textbf{8 (34.8)} & 8 (16.0) & 19 (12.2) & 64 (16.3) & 99 (15.9) & \\
\textit{Candida} spp. & 3 (13.0) & 3 (6.0) & 18 (11.5) & 48 (12.2) & 72 (11.6) & \\
\hline
\end{tabular}
\caption{Distribution [n (%)] of the main organisms isolated from patients with CAB and HAB by age and gender group}
\end{table}

GNFB, Glucose non-fermenting Gram-negative bacilli.
DISCUSSION

The predominant micro-organisms in CAB, HAB and HCAB were strikingly different. *E. coli* was the most common CAB-associated pathogen (42.6 %), and *S. aureus*, *Enterococcus* spp., *E. coli*, *Candida* spp. and *K. pneumoniae* were common pathogens in HAB cases. HCAB showed trends similar to CAB, but the proportion of *E. coli*-associated bacteraemia cases was lower and *P. aeruginosa* was more common in CAB cases (Table 1). HCAB is defined as community-onset but is likely hospital-acquired. The presence of micro-organisms such as *S. aureus* and *P. aeruginosa* is consistent with a healthcare-associated origin of bacteraemia. The predominant bacteraemia-associated pathogens have previously been shown to differ according to study region (Uslan et al., 2007; Kollef et al., 2011; Deen et al., 2012; Huh et al., 2013; Kanoksil et al., 2013). Our study is mostly consistent with recent studies in the USA and north-east Thailand (Uslan et al., 2007; Kollef et al., 2011; Kanoksil et al., 2013). However, our study showed lower proportions of *S. aureus* in CAB cases than those found in studies in the USA and north-east Thailand. *S. aureus* is the second most common cause of CAB in other studies but is less common than *K. pneumoniae* in our study (Table 3). The cause might be related to rare intravenous drug users, and more common pancreatobiliary and liver diseases, which are major causes of CAB due to *K. pneumoniae* in South Korea (Uslan et al., 2007; Jung et al., 2012). *Burkholderia pseudomallei* is a common pathogen found in endemic areas but was rare in our study (Douglas et al., 2004; Kanoksil et al., 2013). *Salmonella enterica* is the most common cause of CAB in low-income countries but was very rare in our study (Reddy et al., 2010; Deen et al., 2012). As the clinical significance of CoNS in bacteraemia-positive blood cultures is difficult to assess, we excluded all CoNS cases in our analysis. Many studies exclude CoNS cases as clinically irrelevant contaminants (Deen et al., 2012; Kanoksil et al., 2013). However, other studies also showed that up to 30% of CoNS can be considered pathogenic, whereas other studies included CoNS cases using their own criteria (Cockerill et al., 2004; Bekeris et al., 2005; Uslan et al., 2007).

As expected, the distributions of organisms were different between the sex and age groups. *E. coli* infection was a strikingly common cause of CAB in females (especially in young adult females). *E. coli* infection may lead to frequent urinary tract infections and pyelonephritis in females, and it was also shown to be the main cause of CAB in females (Uslan et al., 2007). In males, *E. coli*, *K. pneumoniae*, *Streptococcus* spp. and *S. aureus* were the most common pathogens, and males appeared to have various primary infection sites, including the urinary tract, hepatobiliary tract and cardiac valve (Uslan et al., 2007; Jung et al., 2012). *K. pneumoniae* was predominant in middle-aged males – a finding that might be related to the frequency of pancreatobiliary and liver disease, as well as diabetes mellitus, in this demographic (Kang et al., 2006; Jung et al., 2012).

Table 3. Comparison of recent studies on epidemiology of bacteraemia

<table>
<thead>
<tr>
<th>Period</th>
<th>Region</th>
<th>Subjects (N)</th>
<th>Types of bacteraemia</th>
<th>Analysis of subpopulation</th>
<th>Rank of micro-organism*</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003–2005</td>
<td>USA, Minnesota</td>
<td>1051</td>
<td>CAB, HAB, HCAB</td>
<td>Age, sex specific</td>
<td>1. <em>E. coli</em></td>
</tr>
<tr>
<td>2006</td>
<td>USA</td>
<td>1133</td>
<td>CAB, HAB, HCAB</td>
<td>Age, sex specific</td>
<td>2. <em>S. aureus</em></td>
</tr>
<tr>
<td>2008–2012</td>
<td>South Korea</td>
<td>2,956</td>
<td>All bacteraemia</td>
<td>Not done</td>
<td>1. <em>E. coli</em></td>
</tr>
<tr>
<td>2008–2012</td>
<td>South Korea</td>
<td>4,206</td>
<td>CAB</td>
<td>Age, sex specific</td>
<td>2. <em>S. aureus</em></td>
</tr>
</tbody>
</table>

*CoNS are excluded in this table because inclusion criteria for CoNS were variable between studies.
In contrast to CAB cases, the frequency of *E. coli* was comparable to that of *S. aureus* and *Enterococcus* spp. in HAB cases, suggesting that other primary infection sites, in addition to the urinary tract, were common in HAB patients. As older hospitalized patients are often immunocompromised, *Candida* spp. was a frequent pathogen in HAB cases in the advanced-aged group (≥60 years). These findings are similar to those of other studies (Uslan et al., 2007); however, comparison of subgroups is impossible because age- and sex-specific analysis was rarely presented in previous studies (Cockerill et al., 2004).

Most studies have reported the antimicrobial resistance rates without distinguishing between bacteraemia types. A recent surveillance study reported that 18.4 % of *E. coli* and 28.5 % of *K. pneumoniae* were ESBL-positive (Huh et al., 2013). The ESBL rates of *E. coli* and *K. pneumoniae* at our institution are also similar to those in that study, and the reported ESBL-positive rate of *K. pneumoniae* was much higher than that of *E. coli*. However, when we analysed the ESBL rates of CAB and HAB pathogens separately, the ESBL-positive rates of *E. coli* and *K. pneumoniae* were similar and significantly higher in HAB than in CAB (31.3 and 8.8 % for *E. coli*; 33.8 and 8.4 % for *K. pneumoniae*, respectively). The cause of higher ESBL in *K. pneumoniae* may be that a larger fraction of *E. coli* isolates (75.7 %) than *K. pneumoniae* isolates (54.2 %) was community-acquired (CAB). Similarly, the fraction of meticillin-resistant *S. aureus* (MRSA) and vancomycin-resistant enterococci (VRE) were reported to be 63.7 and 24.1 %, respectively, in isolates causing bacteraemia in a recent study in South Korea. However, MRSA and VRE were 37.4 and 5.3 % in CAB and 73.0 and 24.3 % in HAB patients in our data. This rate of MRSA in CAB patients is higher than those reported in studies in Taiwan and Spain (0 and 14 %, respectively) and lower than that found in studies in the USA (56 %) (Wang et al., 2008; Rodriguez-Bañó et al., 2010; Kolfel et al., 2011).

Several limitations of this study should be mentioned. (i) Although this study included a large dataset spanning a recent 5-year period in South Korea, it was from a single university hospital located in Seoul. Thus, our data may not be generalizable to primary institutions and there may be regional differences in South Korea. (ii) Medical histories were obtained through chart review, and information regarding previous hospital admission could be inaccurate, possibly leading to misclassification of some patients.

In conclusion, we demonstrate that CAB and HAB cases show different distributions of associated micro-organisms. The frequencies and types of micro-organisms associated with these cases varied with patient age and sex. We demonstrate antimicrobial susceptibility data on CAB- and HAB-associated pathogens – a finding that may be important for the empirical treatment of bacteraemia.

**ACKNOWLEDGEMENTS**

This study was supported by Konkuk University.

**REFERENCES**


