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국내 3차병원의 혈류감염 발생률에 계절 및 온도가 미치는 영향

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Season and Temperature Effects on **Bloodstream Infection Incidence in a Korean Tertiary Referral Hospital**

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ABSTRACT

Background: The weather has well-documented effects on infectious disease and reports suggest that summer peaks in the incidences of gram-negative bacterial infections among hospitalized patients. We evaluated how season and temperature changes affect bloodstream infection (BSI) incidences of major pathogens to understand BSI trends with an emphasis on acquisition sites.

Methods: Incidence rates of BSIs by Staphylococcus aureus, Enterococcus spp., Escherichia coli, Klebsiella pneumoniae, Acinetobacter spp., and Pseudomonas aeruginosa were retrospectively analyzed from blood cultures during 2008-2016 at a university hospital in Seoul, Korea according to the acquisition sites. Warm months (June-September) had an average temperature of \geq 20 °C and cold months (December–February) had an average temperature of \leq 5 °C.

Results: We analyzed 18,047 cases, where 43% were with community-onset BSI. E. coli (N = 5,365) was the most common pathogen, followed by Enterococcus spp. (N = 3,980), S. aureus (N = 3,075), K. pneumoniae (N = 3,043), Acinetobacter spp. (N = 1,657), and P. aeruginosa (N = 1,010)927). The incidence of hospital-acquired BSI by Enterococcus spp. was weakly correlated with temperature, and the median incidence was higher during cold months. The incidence of community-onset BSI by E. coli was higher in warm months and was weakly correlated with temperature.

Conclusion: We found seasonal or temperature-associated variation in some speciesassociated BSIs. This could be a useful information for enhancing infection control and public health policies by taking season or climate into consideration.

Keywords: Bloodstream infection, Climate change, Incidence, Seasonality



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INTRODUCTION

The weather has well-documented effects on infectious disease patterns [1,2], and there is increased interest in this dynamic with growing concerns about global warming. Because climate change will also impact Korea, it is crucial to elucidate epidemiologic changes of major pathogens to better understand the association between pathogen incidence and seasonal and temperature variations. Summer peaks in the incidences of gram-negative bacterial infections among hospitalized patients have been reported [3-7]. An unusual seasonal pattern of *Acinetobacter calcoaceticus* was reported in the 1970s and in a previous study [5]. We also observed seasonality in community-onset *Acinetobacter baumannii* complex colonization or infection [8]. There is less evidence of seasonal patterns among gram-positive bacteria, but a review of laboratory blood culture data from 1961 to 1981 reported seasonal and monthly variations in *Streptococcus pneumoniae* epidemiology [9]. The impact of temperature change could be different according to acquisition sites, considering well-controlled cooling and heating system in healthcare facilities. In this study, we evaluated trends in the most important clinical isolates according to temperature variability.

MATERIALS AND METHODS

Blood culture analyses

We retrospectively reviewed 18,047 isolates from blood cultures that were carried out from 2008 to 2016 in a university hospital in Seoul, Korea. Incidence rates of bloodstream infections (BSIs) by *Staphylococcus aureus*, *Enterococcus* spp., *Escherichia coli*, *Klebsiella pneumoniae*, *Acinetobacter* spp., and *Pseudomonas aeruginosa* were retrospectively analyzed. We only included pathogens from BSI, such as *S. aureus*, *Enterococcus* spp., *E. coli*, *K. pneumoniae*, *Acinetobacter* spp., and *P. aeruginosa* to definitively exclude colonizers. We analyzed blood cultures from the first isolate strains among those taken from a single patient within 30-day period to eliminate duplicate results. We converted incidence rates to cases/10⁶ patient days for hospital-acquired isolates and cases/10⁵ patient days for community-onset isolates because we wanted to improve readability by making it less decimal. Blood culture was performed with the automated BACT/ ALERT 3D system (bioMérieux, Marcy-l'Étoile, France). Species identification was performed with Bruker MS (Bruker Daltonik, Leipzig, Germany).

Definitions

Warm months (June–September) were those with an average temperature $\geq 20^{\circ}$ C and cold months (December–February) were those with an average temperature $\leq 5^{\circ}$ C. Monthly average temperatures (high) were obtained from the National Weather Service Forecast Office (http://www.kma.go.kr/index.jsp), and we used data, collected at the nearest observation site from the hospital location. We used monthly average temperatures over the study period, according to the previous study [8]. "Hospital-acquired" isolates were those that were obtained after 48 hours of admission, and other isolates obtained within 48 hours of admission, including outpatient isolates, were considered "community-onset (acquired)" [10].

Statistical analyses

The MedCalc Statistical Software version 17.6 (MedCalc Software bvba, Ostend, Belgium; http:// www.medcalc.org; 2017) was used for all statistical analyses. Incidence differences between warm and cold months were compared using the Mann-Whitney test (independent samples). The correlations with temperature were evaluated using Pearson's correlation analysis. In interpretation, we described the extent of correlation according to r value (if r > 0.7, strong; 0.3 = < r = < 0.7, moderate; r < 0.3, week). *P* values <0.05 were regarded as significant.

RESULTS

Total blood culture isolates

We analyzed 18,047 cases from 2008–2016, and 43% of them were community-onset BSIs. *E. coli* (N = 5,365) was the most common pathogen, followed by *Enterococcus* spp. (N = 3,980), *S. aureus* (N = 3,075), *K. pneumoniae* (N = 3,043), *Acinetobacter* spp. (N = 1,657), and *P. aeruginosa* (N = 927).

The ratio of community-onset BSIs/hospital-acquired BSIs (CO/HA) of *E. coli* was 2.4. In contrast, that of *S. aureus, Enterococcus* spp., *Acinetobacter* spp., and *P. aeruginosa* were less than 1 suggesting that most of them were hospital-acquired BSI cases (Table 1).

Table 1. Etiologic agents of bloodstream infections according to acquisition site (2008–2016)

Year	S. aureus			Enterococcus spp.			E. coli			K. pneumoniae			Acinetobacter spp.			P. aeruginosa								
	Total	СО	HA	CO/ HA	Total	СО	HA	CO/ HA	Total	СО	HA	CO/ HA	Total	СО	HA	CO/ HA	Total	СО	HA	CO/ HA	Total	СО	HA	CO/ HA
2008	256	93	163	0.6	368	54	314	0.2	443	313	130	2.4	191	106	85	1.2	160	15	145	0.1	113	44	69	0.6
2009	338	109	229	0.5	365	45	320	0.1	494	340	154	2.2	263	147	116	1.3	247	15	232	0.1	175	50	125	0.4
2010	272	120	152	0.8	395	62	333	0.2	453	328	125	2.6	223	116	107	1.1	144	15	129	0.1	85	32	53	0.6
2011	395	114	281	0.4	508	54	454	0.1	586	346	240	1.4	430	195	235	0.8	164	17	147	0.1	102	47	55	0.9
2012	319	139	180	0.8	347	55	292	0.2	490	358	132	2.7	292	167	125	1.3	202	20	182	0.1	80	22	58	0.4
2013	369	112	257	0.4	508	102	406	0.3	619	461	158	2.9	413	206	207	1.0	240	29	211	0.1	94	30	64	0.5
2014	312	139	173	0.8	476	93	383	0.2	678	497	181	2.7	351	204	147	1.4	167	21	146	0.1	84	23	61	0.4
2015	373	167	206	0.8	461	84	377	0.2	766	559	207	2.7	403	230	173	1.3	171	23	148	0.2	95	35	60	0.6
2016	441	160	281	0.6	552	98	454	0.2	836	596	240	2.5	477	242	235	1.0	162	15	147	0.1	99	44	55	0.8
9 years	3,075	1,153	1,922	0.6	3,980	647	3,333	0.2	5,365	3,798	1,567	2.4	3,043	1,613	1,430	1.1	1,657	170	1,487	0.1	927	327	600	0.5

Abbreviation: CO, community-onset; HA, hospital-acquired.

Staphylococcus aureus and Enterococcus spp.

S. aureus caused a median 17.88 cases per 10^5 patient days of community-onset BSIs (interquartile range, IQR, 13.96–20.92) in warm months and 1.68 (IQR, 15.25–20.37) in cold months (P = 0.6769, Table 2). *S. aureus* caused a median 29.10 cases per 10^6 patient days of hospital-acquired BSIs (IQR, 22.50–37.10) in

warm months and 26.90 (IQR, 20.80–34.70) in cold months (P = 0.6467, Table 3). Neither of the *S. aureus* incidence rates were correlated with temperature (community-onset BSI: correlation coefficient, r = 0.0565, P = 0.5612, 95% confidence interval, 95% CI, -0.1339 to 0.2429; hospital-acquired BSI: r = 0.0444, P = 0.6484, 95% CI, -0.1458 to 0.2314; Fig. 1).

Enterococcus spp. caused a median 0.98 cases per 10^5 patient days of community-onset BSIs (IQR, 0.51–1.48) in warm months and 0.87 (IQR, 0.60–1.26) in cold months (P = 0.6871, Table 2). *Enterococcus* spp. caused a mean 45.20 cases per 10^6 patient days of hospital-acquired BSIs (IQR, 37.90–51.50) in warm months and 57.20 (IQR, 48.90–65.60) in cold months (P = 0.0021, Table 3). The incidence rate of *Enterococcus* spp.-caused community-onset BSI (r = 0.0952, P = 0.3273, 95% CI, -0.0955 to 0.2791) was not correlated with temperature, but the incidence rate of *Enterococcus* spp. of hospital-acquired BSI (r = -0.3020, P = 0.0015, 95% CI, -0.4645 to -0.1199) was weakly correlated with temperature (Fig. 1).

 Table 2. Incidence of community-onset bloodstream infections according to acquisition site and seasonal changes

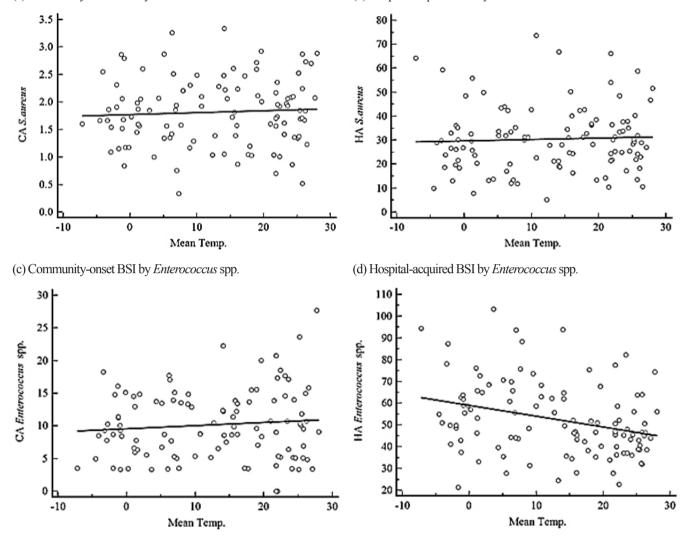
Etiologic agents	Community-onset (cases per 10 ⁵ patient days)										
		Warm mon	ths		Р						
	М	95% CI	IQR	М	95% CI	IQR					
S. aureus	17.88	16.16-20.01	13.96-20.92	16.80	15.63-19.17	15.25-20.37	0.6769				
Enterococcus spp.	0.98	0.61-1.25	0.51-1.48	0.87	0.66-1.12	0.60-1.26	0.6871				
E. coli	60.40	54.90-77.60	53.10-81.30	52.70	47.80-55.80	41.10-61.50	0.0044				
K. pneumoniae	28.20	25.00-32.50	20.90-33.70	22.50	20.10-26.10	17.00-27.90	0.0518				
Acinetobacter spp.	3.34	1.74-4.01	1.68-5.07	1.68	0.00-3.38	0.00-3.84	0.0672				
P. aeruginosa	0.35	0.19-0.70	0.17-0.85	0.40	0.33-0.69	0.31-0.78	0.5976				

Abbreviation: M, median; CI, confidence interval; IQR, interquartile range.

 Table 3. Incidence of hospital-acquired bloodstream infections according to acquisition site and seasonal changes

Etiologic agents	Hospital-acquired (cases per 10 ⁶ patient days)										
		Warm mon	ths		Р						
	М	95% CI	IQR	М	95% CI	IQR					
S. aureus	29.10	24.90-33.70	22.50-37.10	26.90	23.60-32.70	20.80-34.70	0.6467				
Enterococcus spp.	45.20	39.60-47.30	37.90-51.50	57.20	49.80-63.90	48.90-65.60	0.0021				
E. coli	25.40	22.50-30.70	20.60-31.50	24.20	17.10-28.20	16.90-31.20	0.3241				
K. pneumoniae	23.50	18.40-28.40	16.90-30.50	19.80	13.90-25.30	13.70-27.10	0.1965				
Acinetobacter spp.	20.90	17.22-25.69	13.80-27.70	26.60	21.59-28.60	19.70-31.40	0.0956				
P. aeruginosa	8.87	6.74-11.52	5.57-12.70	7.97	5.69-11.55	5.13-12.31	0.3241				

Abbreviation: M, median; CI, confidence interval; IQR, interquartile range.



(a) Community-onset BSI by S. aureus

(b) Hospital-acquired BSI by S. aureus

Fig. 1. Correlation between bloodstream infection (BSI) by gram-positive cocci and average monthly temperature from 2008–2016 based on Pearson's correlation coefficient. (a) Temperature (°C) vs. incidence rate of community-onset BSI by *S. aureus* (cases per 10^5 patient days), y = 0.00337x+1.774, r = 0.0565, P = 0.5612. (b) Temperature (°C) vs. incidence rate of hospital-acquired BSI by *S. aureus* (cases per 10^6 patient days), y = 0.0588x+29.781, r = 0.0444, P = 0.6484. (c) Temperature (°C) vs. incidence rate of community-onset BSI by *Enterococcus* spp. (cases per 10^5 patient days), y = 0.0488x+9.558, r = 0.0952, P = 0.3273. (d) Temperature (°C) vs. incidence rate of hospital-acquired BSI by *Enterococcus* spp. (cases per 10^6 patient days), y = -0.495x+59.061, r = -0.3020, P = 0.0015. CA, community-onset; HA, hospital-acquired; Temp., temperature.

Escherichia coli and Klebsiella pneumoniae

E. coli caused a median of 60.40 cases per 10^5 patient days of community-onset BSIs (IQR, 53.10–81.30) in warm months and 52.70 (IQR, 41.10–61.50) in cold months (*P* = 0.0044, Table 2). *E. coli* caused a median of 25.40 cases per 10^6 patient days of hospital-acquired BSIs (IQR, 20.60–31.50) in warm months and 24.20 (IQR, 16.90–31.20) in cold months (*P* = 0.3241, Table 3). The incidence rate of *E. coli*-caused community-onset BSI (r = 0.3304, *P* = 0.0005, 95% CI 0.1509 to 0.4889) was weakly correlated

with temperature, but the *E. coli* incidence rate for hospital-acquired BSI (r = 0.1443, P = 0.1363, 95% CI, -0.4596 to 0.3244) was not (Fig. 2).

K. pneumoniae caused a median of 28.20 cases per 10^5 patient days of community-onset BSIs (IQR, 20.90–33.70) in warm months and 22.50 (IQR, 17.00–27.90) in cold months (P = 0.0518, Table 2). *K. pneumoniae* caused a median of 23.50 cases per 10^6 patient days of hospital-acquired BSIs (IQR, 16.90–30.50) in warm months and 19.80 (IQR, 13.70–27.10) in cold months (P = 0.1965, Table 3). Neither of the *K. pneumoniae* incidence rates for community-onset BSI (r = 0.1986, P = 0.0394, 95% CI: 0.0099 to 0.3735) nor hospital-acquired BSI (r = 0.1094, P = 0.2596, 95% CI: -0.0812 to 0.2924) was correlated with temperature (Fig. 2).

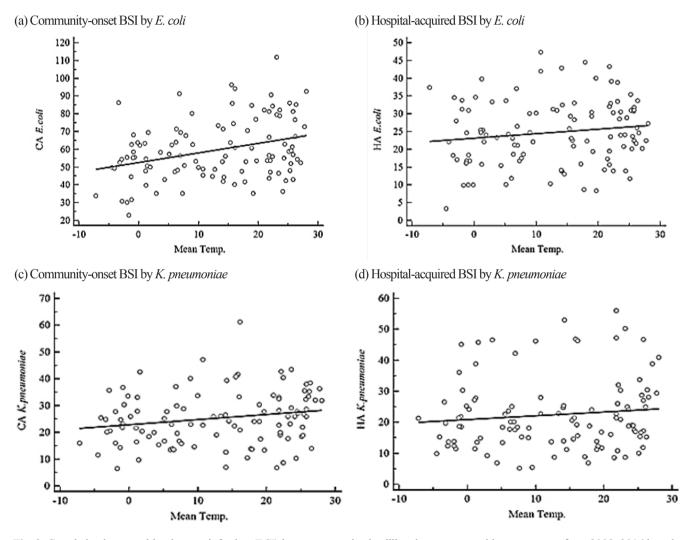


Fig. 2. Correlation between bloodstream infection (BSI) by gram-negative bacilli and average monthly temperature from 2008–2016 based on Pearson's correlation coefficient. (a) Temperature (°C) vs. incidence rate of community-onset BSI by *E. coli* (cases per 10⁵ patient days), y = 0.540x+52.754, r = 0.3304, P = 0.0005. (b) Temperature (°C) vs. incidence rate of hospital-acquired BSI by *E. coli* (cases per 10⁶ patient days), y = 0.128x+23.142, r = 0.1443, P = 0.1363. (c) Temperature (°C) vs. incidence rate of community-onset BSI by *K. pneumoniae* (cases per 10⁵ patient days), y = 0.193x+22.874, r = 0.1986, P = 0.0394. (d) Temperature (°C) vs. incidence rate of hospital-acquired BSI by *K. pneumoniae* (cases per 10⁶ patient days), y = 0.124x+20.931, r = 0.1094, P = 0.2596. CO, community-onset; HA, hospital-acquired; Temp., temperature.

Acinetobacter spp. and Pseudomonas aeruginosa

Acinetobacter spp. caused a median of 3.34 cases per 10^5 patient days of community-onset BSIs (IQR, 1.68–5.07) in warm months and 1.68 (IQR, 0.00–3.84) in cold months (P = 0.0672, Table 2). Acinetobacter spp. caused a median of 20.90 cases per 10^6 patient days of hospital-acquired BSIs (IQR, 13.80–27.70) in warm months and 26.60 (IQR, 19.70–31.40) in cold months (P = 0.0956, Table 3). Neither of the Acinetobacter spp. incidence rates for community-onset BSI (r = 0.2100, P = 0.0292, 95% CI, 0.0219 to 0.3837) nor hospital-acquired BSI (r = -0.1148, P = 0.2368, 95% CI, -0.2973 to 0.0758) was correlated with temperature (Fig. 3).

P. aeruginosa caused a median of 0.35 cases per 10^5 patient days of community-onset BSIs (IQR, 0.17–0.85) in warm months and 0.40 (IQR, 0.31–0.78) in cold months (P = 0.5976, Table 2). *P. aeruginosa*

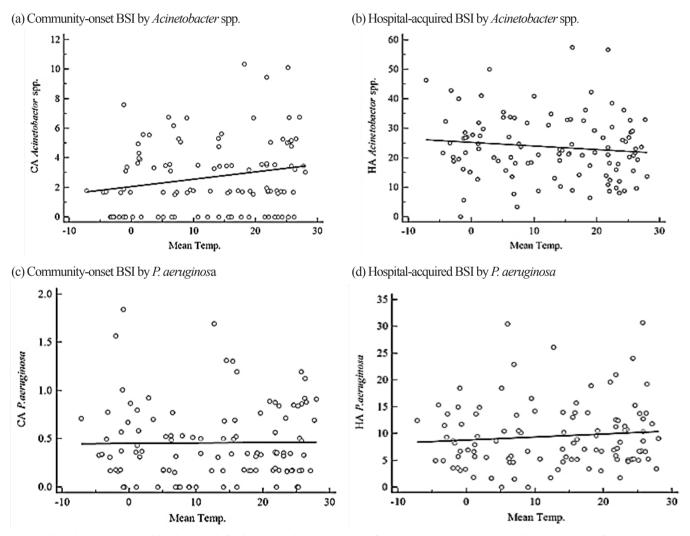


Fig. 3. Correlation between bloodstream infection (BSI) by glucose non-fermenters and average monthly temperature from 2008–2016. (a) Temperature (°C) vs. incidence rate of community-onset BSI by *Acinetobacter* spp. (cases per 10^5 patient days), y = 0.0500x+2.065, r = 0.2100, P = 0.0292. (b) Temperature (°C) vs. incidence rate of hospital-acquired BSI by *Acinetobacter* spp. (cases per 10^6 patient days), y = -0.121x+25.202, r = -0.1148, P = 0.2368. (c) Temperature (°C) vs. incidence rate of community-onset BSI by *P. aeruginosa* (cases per 10^5 patient days), y = 0.000520x+0.455, r = 0.0137, P = 0.8879. (d) Temperature (°C) vs. incidence rate of hospital-acquired BSI by *P. aeruginosa* (cases per 10^6 patient days), y = 0.0565x+8.814, r = -0.0957, P = 0.3241. CO, community-onset; HA, hospital-acquired; Temp., temperature.

caused a median of 8.87 cases per 10^6 patient days of hospital-acquired BSIs (IQR, 5.57–12.7) in warm months and 7.97 (IQR, 5.13–12.31) in cold months (P = 0.3241, Table 3). Neither of the *P. aeruginosa* incidence rates for community-onset BSI (r = 0.0137, P = 0.8879, 95% CI, -0.1757 to 0.2022) nor hospital-acquired BSI (r = -0.0957, P = 0.3241, 95% CI, -0.0949 to 0.2797) was correlated with temperature (Fig. 3).

DISCUSSION

Summer peaks in the incidences of gram-negative bacterial infections relative to gram-positive infections among hospitalized patients have been reported [3-7]. We found no correlation between temperature and the incidence of community-onset *S. aureus* BSI, hospital-acquired *S. aureus*, or community-onset *Enterococcus* spp. BSI. However, the incidence of *Enterococcus* spp. of hospital-acquired BSI was weakly correlated with temperature, and the median value of *Enterococcus* spp.-caused hospital-acquired BSIs was higher in cold months. These results are particularly interesting, considering that the temperatures of healthcare facilities are relatively well controlled. Further studies are needed to evaluate other risk factors of hospital-acquired *Enterococcus* spp. BSIs.

The widespread presence of ESBL-producing *E. coli* in the community is well established due to the worldwide increase of the sequence type (ST) 131 clone in the mid 2000s [11]. We also found a high prevalence of ESBLs mainly CTX-M among the community-onset *E. coli* isolates from Korean community hospitals [12]. Recently, community-onset *E. coli* infections and asymptomatic carriage in healthy individuals without recent exposure to healthcare facilities have increased [13]. Multiple sources of community-based multiple drug-resistant *E. coli* have been suspected recently, including among livestock, companion animals, sewage, wastewater, and recreational waterways [14]. We observed a higher incidence of community-onset *E. coli* BSI in warm months, but this trend was not observed with the hospital-acquired *E. coli* BSIs. *E. coli* was the most common causative agent of community-onset BSIs. We think that it is a possible reason why community-onset *E. coli* BSIs showed seasonality in this study. Microorganisms in the community or environment could be more easily affected by temperature than those in healthcare facilities. Therefore, it is easier to observe seasonality in isolates from community, considering that the temperature varies widely than that of the healthcare facilities.

Regarding glucose non-fermenters, there is some evidence of seasonality in *A. baumannii* infections [3,4,8]. We found that the median number of BSIs by *Acinetobacter* spp. was not different between warm months and cold months, regardless of hospital-acquired or community-onset infection acquired site. Furthermore, the *Acinetobacter* spp. BSI incidence rate was not correlated with temperature. This result is inconsistent with our previous study, which showed a seasonal pattern for community-onset *A. baumannii* complex colonization or infection [8]. The discrepancy may be due to the different study designs we employed because the previous study included all infection types, while only BSIs were included in this study. Although extra-hospital reservoirs of *A. baumannii* complex have been suspected [15], *A. baumannii* primarily causes healthcare-associated infection. *A. baumannii* isolates dramatically increased in Korean hospitals [16]. Hospital-acquired A. *baumannii* complex isolation is highly clonal, indicating that the

incidence of healthcare-onset cases may have been affected by the endemic nature of Korean hospitals. The median number of *P. aeruginosa* BSIs was not different between warm and cold months, regardless of the infection site. The *P. aeruginosa* BSI incidence rate was not correlated with temperature.

Although seasonal patterns of gram-negative organisms have been observed, the mechanisms underlying seasonal variation are not well understood. A possible explanation is that higher temperatures may facilitate increased bacterial growth in the environment as well as enhanced virulence of gram-negative bacteria, thereby contributing to increases in infection incidence in warmer periods [17]. Another explanation is that the lipidA moiety of lipopolysaccharides, which forms the outer monolayer of the outer membrane of most gram-negative bacteria, is regulated by environmental conditions [18]. Recently, it was reported that the carbapenemase gene, KPC showed the highest frequency of gene transfer at 25°C and NDM at 30°C, which suggested temperature was related to plasmid transfer frequency [19].

There are some limitations as a single-center study, and thus, further study is required in diverse clinical settings. However, we found that *E. coli* (N = 5,365) was the most commonly isolated from BSI, followed by *Enterococcus* spp. (N = 3,980), *S. aureus* (N = 3,075), *K. pneumoniae* (N = 3,043), *Acinetobacter* spp. (N = 1,657), and *P. aeruginosa* (N = 927), which was consistent with previous studies [20-22]. Based on this data, we think that bias was unlikely as a single agency study.

In conclusion, we found seasonal or temperature-associated variation in BSIs according to some species. Our findings could be useful information for enhancing infection control and public health policies that take season or climate into consideration. The enhancement of infection control and public health policies, taking season or climate into consideration could be needed.

요약

배경: 감염질환의 빈도가 날씨에 따라 달라지며, 입원환자에서 여름철에 그람음성 세균 감염이 증가한다는 것이 알려져 있다. 본 연구에서는 주요 병원균에 의한 혈류감염의 빈도가 계절 및 온 도에 따라 달라지는지, 지역사회 감염과 병원감염을 나누어 평가하고자 하였다.

방법: 2008~2016년 서울의 한 대학병원에서 발생한 *Staphylococcus aureus*, *Enterococcus* spp., *Escherichia coli*, *Klebsiella pneumoniae*, *Acinetobacter* spp. 및 *Pseudomonas aeruginosa*에 의한 혈류감 염을 후향적으로 분석하였다. 여름(6~9월)은 평균 온도가 20℃ 이상으로, 겨울 (12~2월)은 평균 온 도가 5℃ 미만으로 정의하였다.

결과: 지역사회 발생 E. coli 혈류감염이 총 18,047건 중 43% (N = 5,365)를 차지하여 가장 흔했고, Enteroccus spp. (N = 3,980), S. aureus (N = 3,075), K. pneumoniae (N = 3,043), Acinetobacter spp. (N = 1,657), 및 P. aeruginosa에 의한 혈류감염 (N = 927) 순이었다. 병원에서 발생한 Enteroccus spp. 혈류 감염은 온도와 약한 상관관계를 보였고, 추운 달에 발생률이 더 높았다. 지역사회 발생 E. coli 혈 류감염은 여름에 발생률이 더 높았고, 온도와 약하게 상관관계가 있었다.

결론: 일부 균종에서 혈류감염의 발생이 계절적 또는 온도와 연관됨을 알 수 있었다. 이는 계절이 나 기후를 고려한 감염 관리 및 공중 보건 정책을 강화하는 데 유용한 정보가 될 수 있다.

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