Seasonal Variation in *Klebsiella pneumoniae* Bloodstream Infection on 4 Continents

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Background. *Klebsiella pneumoniae* causes serious, life-threatening infections in humans in endemic and epidemic settings. The objective of this study was to determine whether the incidence of *K. pneumoniae* bloodstream infection (BSI) was higher during warm months.

Methods. We analyzed surveillance data from 2001–2006 at 4 hospitals located on 4 continents. Incidence rates (IRs) and IR ratios (IRRs) were determined using multivariable Poisson regression.

Results. In total, 1189 cases of *K. pneumonia* BSIs occurred during 6,671,337 patient-days. The IR of *K. pneumoniae* BSI during the 4 warmest months of the year was 2.23/10,000 patient-days, whereas the IR of *K. pneumoniae* BSI for the other 8 months was 1.55/10,000 patient-days (IRR, 1.46 [95% confidence interval, 1.04–2.06]; $P = .03$). In contrast, no seasonal variation was identified in rates of BSI due to *Enterobacter* or *Serratia* species. Using Poisson regression, we showed that temperature ($P < .0001$) and dew point (a marker for relative humidity; $P < .0001$) were both linearly predictive of increasing rates of *K. pneumoniae* BSI.

Conclusions. Environmental pressures may lead to an increase in the IR of *K. pneumoniae* BSI during the warmest months of the year.

Klebsiella pneumoniae is a ubiquitous environmental organism and a common cause of serious gram-negative infections in humans, including bloodstream infection (BSI), ventilator-associated pneumonia, and urinary tract infection [1–3]. Infections due to *K. pneumoniae* occur in both endemic and outbreak settings [3, 4]. Isolates of *K. pneumoniae* are becoming increasingly resistant to antibiotics and subsequently may become even more difficult to treat. For example, 21% of *K. pneumoniae* infections in US intensive care units were resistant to third-generation cephalosporins in 2003 [5].

Some gram-negative organisms, including *Acinetobacter* [6] species, *Aeromonas* species [7, 8], and *Burkholderia pseudomallei* [9], have seasonal variations in rates of infection. Although veterinarians have noted that *K. pneumoniae* intramammary infections in cows are increased during summer [10], seasonal variation in the incidence of *K. pneumoniae* infection in humans has not, to our knowledge, been reported. By a systematic examination of the incidence of pathogens in a large hospital in Marseille, we found a significant increase in BSI caused by *K. pneumoniae* during the summer months. The objective of the present study was to evaluate this observation further and specifically to determine whether *K. pneumoniae* BSI has a higher incidence during warm months in 4 countries located on 4 continents. In addition, we examined the rates of *Serratia* and *Enterobacter* BSIs to assess whether similar seasonal variations occurred with these organisms.

METHODS

We conducted a retrospective ecological study using microbiological data from 4 tertiary referral institutions on 4 continents: Duke University Medical Center (DUMC) in Durham, North Carolina (35°59' N, 78°54' W); Assistance Publique–Hôpitaux de Marseille (APHM) in Marseille, France (43°18' N, 5°23' E); the Bayside Health (BH) hospital network in Melbourne, Australia (37°49' S, 144°57' E); and Koo Foundation Sun Yat-Sen Cancer
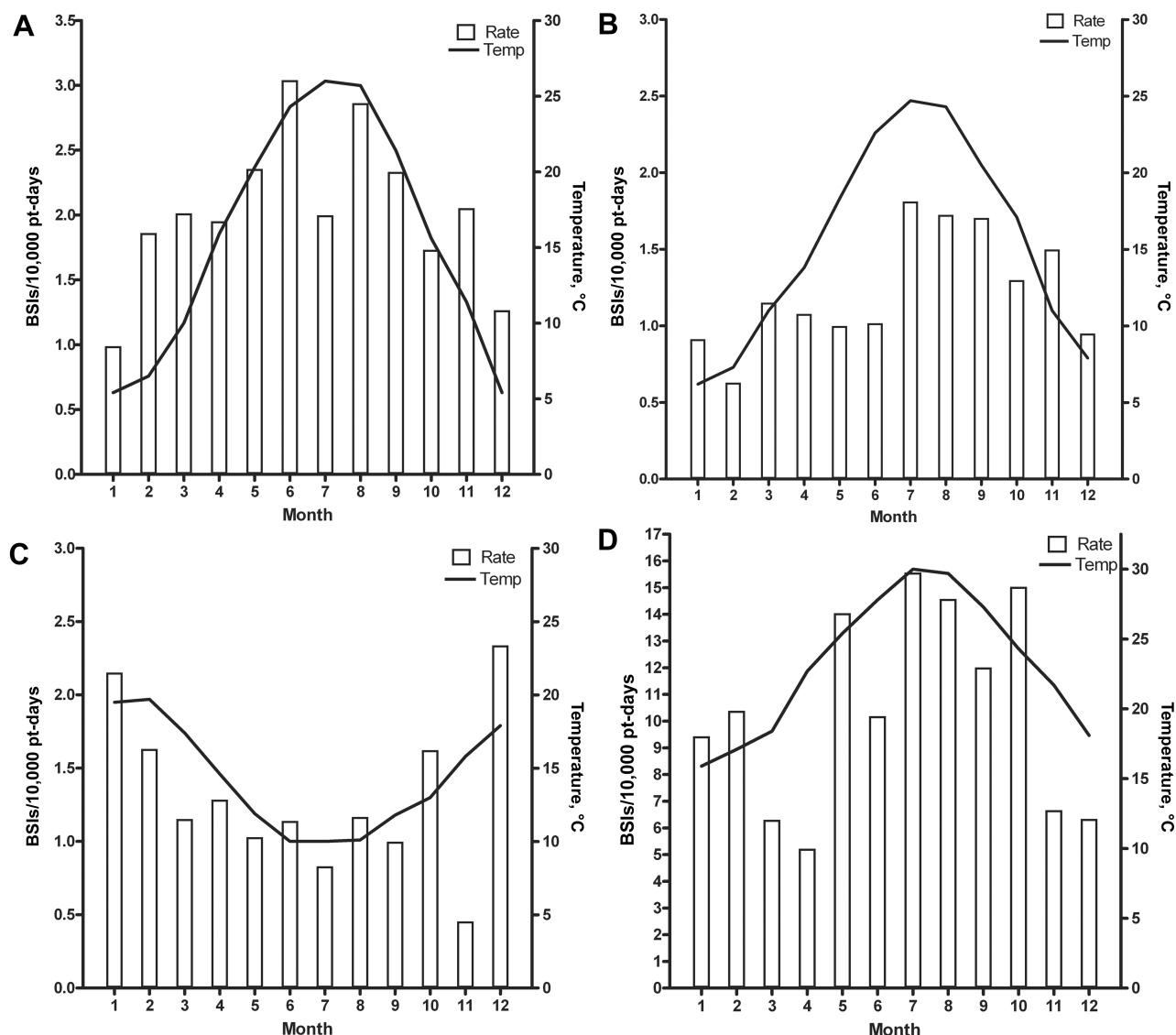
Figure 1. Monthly rates of *Klebsiella pneumoniae* bloodstream infection (BSI) and average monthly temperatures at 4 study institutions on 4 continents. *A,* Duke University Medical Center, Durham, North Carolina. *B,* Assistance Publique–Hôpitaux de Marseille, Marseille, France. *C,* Bayside Health, Melbourne, Australia. *D,* Koo Foundation Sun Yat-Sen Cancer Center, Taipei, Taiwan. pt-days, patient-days.

Center (KFSYSCC) in Taipei, Taiwan (25°01′ N, 121°27′ E). All study institutions are located in temperate regions of the globe with distinct seasons throughout the year. Taipei, however, has a perennial mild subtropical weather pattern that is interrupted briefly by summer typhoons.

DUMC is a 753-bed university-affiliated center with 8 intensive care units, a trauma unit, and a bone marrow transplant unit. Patient-day and BSI incidence data for the 3 study organisms (*K. pneumoniae* and *Enterobacter* and *Serratia* species) were available at DUMC from January 2001 to December 2006.

APHM is a network of 3 hospitals (Hôpitaux de la Timone, Conception, and Sud) with 2864 beds. *K. pneumoniae* BSI and patient-day data were available at APHM from January 2001 to September 2006. *Enterobacter* and *Serratia* BSI data were available from January 2002 to December 2006.

BH is a network of 3 hospitals (Alfred Hospital, Sandringham Hospital, and Caulfield Hospital) with 796 beds. The Alfred Hospital offers statewide specialty services that include intensive care, burn, trauma, and transplantation units. Sandringham and Caulfield Hospitals comprise a total of 446 beds that provide community-level obstetrics, emergency medicine, hemodialysis, rehabilitation, and assisted accommodation. *K. pneumoniae* BSI and patient-day data were available at BH from January 2002 to November 2006. *Enterobacter* and *Serratia* BSI data were available from June 2002 to November 2006.

KFSYSCC is a 352-bed university-affiliated cancer center located in Taipei, Taiwan. *K. pneumoniae* BSI, *Enterobacter* BSI, *Serratia* BSI, and patient-day data were available at KFSYSCC from January 2002 to December 2006.

Table 1. Incidence rates (IRs) and IR ratios (IRRs) for *Klebsiella pneumoniae* bloodstream infection (BSI) during the warm season compared with the rest of the year, for 4 hospitals on 4 continents.

Hospital	IR (95% CI) Warm season	IR (95% CI) Rest of year	IRR (95% CI)	P
KFSYSCC	13.1 (4.13–22.9)	9.18 (0–21.7)	1.41 (1.02–1.95)	.04
DUMC	2.56 (0.65–4.63)	1.78 (0.48–3.32)	1.44 (1.11–1.87)	.006
BH	1.79 (0.36–4.29)	1.07 (0–2.62)	1.49 (1.00–2.22)	.05
APHM	1.56 (0.55–3.70)	1.05 (0.19–2.23)	1.47 (1.13–1.89)	.004

NOTE. IRs were calculated as the no. of *K. pneumoniae* BSIs/10,000 patient-days; IRs, IRRs, 95% confidence intervals (CIs), and *P* values were obtained using Poisson regression. The warm season was defined as the 4 warmest months of the year at each location. APHM, Assistance Publique–Hôpitaux de Marseille (Marseille, France); BH, Bayside Health (Melbourne, Australia); DUMC, Duke University Medical Center (Durham, North Carolina); KFSYSCC, Koo Foundation Sun Yat-Sen Cancer Center (Taipei, Taiwan).

Variables and definitions. A BSI was defined as ≥1 blood culture from a patient that was positive for a study organism *(K. pneumoniae, Enterobacter* species, or *Serratia* species). A patient-day was defined as any portion of a day during which a patient received inpatient care at a study institution. Incidence rates (IRs) of BSI were calculated per 10,000 patient-days. The warm season was defined as the 4 warmest months in a calendar year at each institution. In Durham, Marseille, and Taipei, the warm season spanned June–September; in Melbourne, the warm season included December–March. To calculate composite monthly rates, the Southern Hemisphere calendar was transposed to equate the Northern Hemisphere calendar. For example, January in Australia was considered to be equivalent to July in the United States or France.

Average monthly temperatures, average monthly dew point (the temperature at which water vapor condenses—a marker of relative humidity), average monthly precipitation, and average monthly barometric pressure for 2001–2006 were obtained from local airport almanac data at each site.

Statistical analysis. All analyses were performed using SAS (version 9.1). Rates were compared using the *z* statistic; 95% confidence intervals (CIs) were calculated for each rate. Linear regression was used to determine trends among rates of *K. pneumoniae* BSI and relative rates. Multivariable linear regression was performed using a Poisson distribution with stepwise selection. Stepwise selection is a method for determining the best model fit by sequentially adding individual variables to the basic model (dependent and independent variable) and determining partial contribution of each variable to the overall model. The final model consisted of all variables that made a significant contribution to the overall model ($P < .05$). Patient-days were normalized by log transformation, and quadratic terms were included in the model. Effect-measure modification was evaluated using interaction terms. For all tests, differences were considered significant at $P \leq .05$.

RESULTS

A total of 1189 cases of *K. pneumonia* BSI were identified during 6,671,337 patient-days during the study period (overall IR, 1.78/10,000 patient-days). Data were available for a total of 260 months. The overall mean monthly IR was 3.60/10,000 patient-days (95% CI, 0.18–15.8). The mean monthly IRs for the 4 institutions were as follows: KFSYSCC, 10.5/10,000 patient-days (95% CI, 0.97–22.5); DUMC, 2.04/10,000 patient-days (95% CI, 0.49–4.36); BH, 1.30/10,000 patient-days (95% CI, 0–3.45); and APHM, 1.23/10,000 patient-days (95% CI, 0.35–2.57). The mean monthly IR was significantly higher at KFSYSCC than at the other 3 institutions ($P < .0001$, for all comparisons). Similarly, the mean monthly IR was significantly higher at DUMC than at BH ($P = .0002$) or APHM ($P < .0001$); the mean monthly IRs at APHM and BH were not significantly different ($P = .83$).

Trends in monthly rates for each institution and the average monthly temperatures are summarized in figure 1*A*–1*D*. The average ± SD monthly temperatures during the study period were 23.1°C ± 5.0°C at KFSYSCC, 15.6°C ± 7.7°C at DUMC, 15.2°C ± 6.9°C at APHM, and 13.9°C ± 3.7°C at BH. IRs of *K. pneumoniae* BSI were consistently 1.5 times higher during the warm season than during the rest of the year at all 4 hospitals (table 1).

The composite rates were highest during the 4 warmest months of the year (figure 2). The IR of *K. pneumoniae* BSI during the warm season was 2.23/10,000 patient-days, compared with 1.55/10,000 patient-days for the other 8 months of the year. Overall, the rate of *K. pneumoniae* BSI was ~1.5 times higher during the 4 warmest months of the year (IR ratio [IRR], 1.46 [95% CI, 1.04–2.06]; $P = .03$).

Multivariable linear regression with stepwise selection was performed to determine predictors for increases in the IR of *K. pneumoniae*. Temperature ($P < .0001$) and dew point (a marker for relative humidity; $P < .0001$) were both linearly
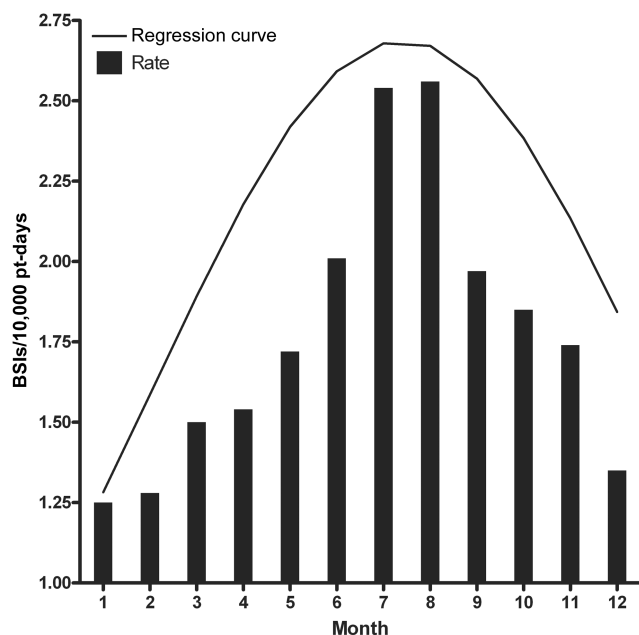
Figure 2. Multivariable regression curve and composite monthly incidence rates for *Klebsiella pneumoniae* bloodstream infection (BSI) at 4 hospitals on 4 continents. A multivariable linear regression model with stepwise selection was created to determine composite rates of infection while controlling for temperature, humidity, and hospital. Months at the Bayside Health hospitals in Australia were transposed to mirror months in the Northern Hemisphere; for example, July in the Southern Hemisphere was made equivalent to January (month 1) in the Northern Hemisphere. pt-days, patient-days.

predictive of increasing rates of *K. pneumoniae* BSI. Barometric pressure, rainfall, and month were not predictive and were not included in the final model. No other predictor variables were analyzed.

Neither *Enterobacter* nor *Serratia* BSI showed seasonal variation in IRs (figure 3). The IR of *Enterobacter* BSI at the 4 study institutions was 1.39/10,000 patient-days during the warm season and 1.15/10,000 patient-days during the rest of the year (IRR, 1.22 [95% CI, 0.92–1.63]; $P = .16$). Similarly, the IR of *Serratia* BSI at the 4 study institutions was 0.39/10,000 patient-days during the warm season and 0.32/10,000 patient-days during the rest of the year (IRR, 1.23 [95% CI, 0.86−1.77]; $P = .26$).

DISCUSSION

Our epidemiological analysis of 1189 cases of *K. pneumonia* BSIs during 6,671,337 patient-days is the first to describe a seasonal variation in the IR of *K. pneumoniae* BSI in humans. The rate of *K. pneumoniae* BSI was 1.5 times higher during the 4 warmest months of the year at 4 institutions located on 4 continents. In contrast, no seasonal variation was identified in rates of BSI due to *Enterobacter* or *Serratia* species, organisms in the family Enterobacteriaceae believed to be most similar to *Klebsiella* species.

Our data suggest that rates of *K. pneumoniae* BSI were significantly associated with changes in temperature and humidity. Several previously described characteristics of *K. pneumoniae* support our findings. First, *K. pneumoniae* is the most heat tolerant of all enteric pathogens [11]. Second, the specific growth rate of *K. pneumoniae* is maximal at temperatures approaching 36.9°C [12, 13]. Finally, *K. pneumoniae* survives better at higher humidity, as experimental models have shown that dehydration is an important factor in inactivating the organism [14].

The exact cause for the observed higher rates of *K. pneumoniae* BSI during warm months remains elusive. *K. pneumoniae* is found naturally in 2 habitats: in environmental settings, such as water, sewage, soil, and plants, and on the mucosal surfaces of mammals [1, 3]. The density of *K. pneumoniae* in the environment (e.g., in freshwater ponds) is higher during warm months [15]. Furthermore, the density of *K. pneumoniae* is higher in cow feces during the summer [16], and *K. pneumoniae* mammary infections in cows are more common during summer [10]. Thus, it is reasonable to hypothesize that humans also have higher levels of colonization with environmental *K. pneumoniae* during warm months. These environmental *K. pneumoniae* isolates are just as virulent as clinical isolates from hospitals and can produce important virulence factors [17, 18]. Furthermore, intestinal colonization typically precedes infection in humans [19], and hospitalized patients with *K. pneumoniae* colonization are at 4-fold higher risk of *K. pneumoniae* infection than noncarriers [20]. Thus, increased colonization leading to infection may explain the observed increase in infection rate in summer.

Our study has limitations. The majority of our data were obtained from tertiary referral centers. Thus, conclusions from our study may not be generalizable to all hospitals, because of refer-
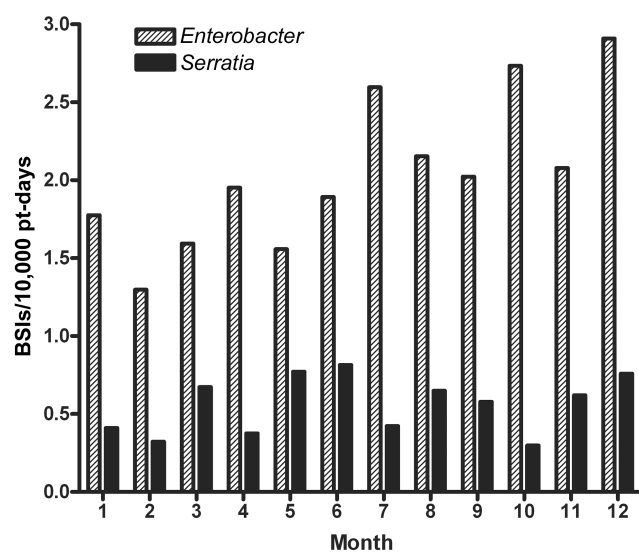

Figure 3. Monthly incidence rates of *Enterobacter* and *Serratia* bloodstream infection (BSI) at 4 study institutions on 4 continents. pt-days, patient-days.

ral bias. Our study includes data from health networks that served different populations and may have adhered to dissimilar standards of medical practice. In particular, KFSYSCC is an oncology specialty center. Patients with either solid-organ or hematologic cancers are at higher risk for infection due to *K. pneumoniae* [21]. Furthermore, this hospital is located in Taiwan, where *K. pneumoniae* is a leading cause of infection [22]. Nevertheless, our results had remarkable internal consistency, because the IRRs comparing warm months with the rest of the year were similar at all hospitals. Finally, our study represents an epidemiological survey. As such, we were unable to analyze specific patient characteristics or diseases that might have contributed to the observed trends.

Future studies are needed to determine the reasons for the seasonal variation of *K. pneumoniae* BSI that we observed. For example, future studies of the epidemiology of *K. pneumoniae* infection should include season, temperature, and humidity as important covariables and possible confounders. Furthermore, future investigations of outbreaks of *K. pneumoniae* should consider the environment as either a source of clonal spread in the hospital or a contributing factor. Finally, groups at high risk for colonization with gram-negative organisms, such as alcoholics [23], those with diabetes [24], and intubated patients [25], could be analyzed prospectively to determine whether rates of *K. pneumoniae* colonization vary with temperature as well.

Clinicians and infectious disease physicians alike must remain informed about the infections that affect their patients, as the epidemiology of infections will continue to change in the 21st century. *K. pneumoniae* is becoming more resistant and more difficult to treat. Our large survey adds novel information to the changing epidemiology of *K. pneumoniae.* Our data suggest that *K. pneumoniae* is an important pathogen in hospitals worldwide and that rates of *K. pneumoniae* BSI vary seasonally. Finally, this study resulted from the implementation of surveillance tools to detect abnormal events in infectious disease. This method of surveillance may lead to other surprising discoveries.

Acknowledgments

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