Seasonal variation of hospital-acquired bloodstream infections: a national seasonality cohort study

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Appendix 1. Surveillance programme bloodstream infection (BSI) case definition

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| **BSI Criteria** |
| Recognized pathogen isolated from ≥1 blood culture |
| Common skin commensal\* cultured from ≥2 blood cultures drawn on separate occasions (within 3 days of each other) *and* at least one of the following clinical symptoms within 24 hours of the positive culture:  1. ≥12 months: fever (>38°C), chills, or hypotension  2. <12 months: fever (>38°C), hypothermia (<36.5°C), apnea (5 sec), bradycardia (<80/min) |
| For neonates (≤28 days): ≥1 positive blood culture for coagulase-negative staphylococcus (≥2 days after birth) *and*  1. ≥2 of the following: fever (>38°C), unstable temperature, hypothermia (<36.5°C), tachycardia (>200/min), bradycardia, capillary refill >2 sec, apnea, unexplained metabolic acidosis (BE ≤ 10mEq/L), new-onset hyperglycemia (>140mg/dL), or other signs (skin colour, increased respiratory support, apathy, hemodynamic instability) *and*  2. ≥1 of the following: CRP >2.0mg/dL, neutrophil ratio I/T > 0.2, leukopenia <5/nL, or thrombopenia <100/nL |

\* Organisms that constitute normal skin flora include diphteroids, Bacillus sp., Propionibacterium sp., coagulase-negative staphylococci [CoNS], or micrococci.

Appendix 2. Surveillance programme central line-associated bloodstream infection (CLABSI) definition criteria

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| **CLABSI Criteria in 2000–2012** |
| **Confirmed**: Bloodstream infection with a concomitant positive culture of the catheter tip, using one of the following semi-quantitative methods:  1. ≥15 colony forming units (CFU) in a semi-quantitative culture (24h incubation) on a catheter segment (5–7cm) rolled over a blood agar (roll-plate Maki method)  2. >103 colonies (CFU) per intradermal catheter segment (1cm), washed with a liquid blood agar by ‘flushing’ or ‘vortex’ after semi-quantitative culturing of the flushing medium  3. ‘Paired samples’: the same microorganisms (species and antibiogram) are cultured from a peripheral vein sample and catheter with, in a quantitative culture, the number of CFUs in catheter / number of CFUs peripheral blood >5  **Probable**: However, if one of the three previous criteria are not satisfied but the bloodstream infection is still considered to be related to the central venous catheter, it can be noted as a probable central line-associated bloodstream infection. |
| **CLABSI Criteria in 2013–2014** |
| A central line-associated bloodstream infection is a BSI where a central line was in place during the 2 calendar days before the onset of infection *and* no other cause of infection can be identified |

**Appendix 3. Statistical methodology for mixed-effects negative binomial regression analysis**

A Poisson-type distribution model was chosen above linear regression because the dependant variable, hospital-acquired bloodstream infections (HABSI) per patient days, was not normally distributed. A negative binomial distribution was applied in place of a Poisson distribution because the number of quarterly infections was overdispersed: the variance (i.e. the square of the standard deviation) of quarterly HABSI per hospital was greater than the mean.

The mixed-effects negative binomial distribution regression model estimated the adjusted incidence rate ratio (IRR) with 95% confidence intervals (CI) to identify a significant peak-to-low ratio in monthly and seasonal HABSI rates. The month and year variables were applied as categorical variables. The model adjusts for confounding factors such as year, acute versus chronic care hospital, and university-affiliated hospital status (fixed effects). Monthly number of patient days was included as an exposure variable to adjust for the fact that with increased exposure, there is an increased risk of HABSI development. Varying hospital participation and characteristics, such as differing baseline infection rates and patient populations, which could not be further quantified were accounted for by applying the hospital units as random effects. Bed size was not included in the regression analysis model because of non-significance. The mixed-effects negative binomial distribution regression model was also applied to analyse associations between climate and HABSI incidence rates. One model estimated the year-round adjusted IRR with correction for temperature, humidity, precipitation, season, year, university-affiliated hospital status, infection risk exposure, and hospital units as random-effects. If the year-round model identified significant associations with climate, a second model was performed to analyse climate associations within seasons by applying weather-by-season interaction terms: temperature-by-season and humidity-by-season.

The mixed-effects regression analyses were stratified per microorganism species and HABSI per infectious focus. Graphs were created to visually display the absolute rate changes based on the results of the relative IRRs of the regression analysis. To create the figures based on the estimated adjusted IRR, the statistical post-estimation function *predict* calculated the estimated average infections per hospital month (with respect to the results of the fixed and random effects). Fixed and random effects were tested using the Wald and likelihood-ratio test.

**Appendix 4. Number of hospital-acquired bloodstream infections, per microorganism and infectious origin**

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| HABSI | Number | % |
| Per microorganism |  |  |
| Gram-positive bacteria | 23 870 | 48.7 |
| CNS | 8731 | 17.8 |
| *S. aureus* | 5675 | 11.6 |
| *E. faecalis* | 2426 | 4.9 |
| *E. faecium* | 1096 | 2.2 |
| *S. pneumoniae* | 725 | 1.5 |
| Viridansstreptococci | 792 | 1.6 |
| Gram-negative bacteria | 21 472 | 43.8 |
| *E. coli* | 9010 | 18.4 |
| *P. aeruginosa* | 2578 | 5.3 |
| *K. pneumoniae* | 2405 | 4.9 |
| *E. cloacae* | 1653 | 3.4 |
| *K. aerogenes* | 1205 | 2.5 |
| *Proteus* spp. | 1130 | 2.3 |
| *K. oxytoca* | 1115 | 2.3 |
| *Acinetobacter* spp. | 968 | 2.0 |
| *Serratia* spp. | 860 | 1.8 |
| *Bacteroides* spp. | 844 | 1.7 |
| *Morganella* spp. | 469 | 1.0 |
| *Citrobacter* spp. | 374 | 0.8 |
| *Stenotrophomonas* spp. | 262 | 0.5 |
| *Candida* spp. | 2826 | 5.8 |
| *C. albicans* | 1587 | 3.2 |
| *Candida* *non-albicans* | 1239 | 2.6 |
| Per infectious origin |  |  |
| Central line | 8618 | 17.6 |
| Urinary tract | 7266 | 14.8 |
| Pulmonary | 4711 | 9.6 |
| Intra-abdominal | 4124 | 8.4 |
| Deep surgical site | 1452 | 3.0 |
| Skin and soft tissue | 1387 | 2.8 |
| Unknown | 16 713 | 34.1 |
| HABSI: Hospital-wide includes hospital-acquired bloodstream infections. CNS: coagulase-negative staphylococci. | | |

**Appendix 5. Hospital-acquired bloodstream infections, number of microorganisms per infectious origin**

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| HABSI | Number | % |
| Central line |  |  |
| CNS | 3986 | 47.2 |
| Gram-negative bacteria | 1745 | 20.2 |
| *S. aureus* | 1242 | 14.7 |
| *Candida* spp. | 918 | 10.8 |
| Urinary tract |  |  |
| *E. coli* | 3465 | 48.3 |
| *Klebsiella* spp. | 891 | 12.4 |
| Other Enterobacterales | 715 | 8.1 |
| *P. aeruginosa* | 465 | 6.5 |
| *S. aureus* | 401 | 4.2 |
| *E. cloacae* | 211 | 2.9 |
| Pulmonary |  |  |
| *S. aureus* | 683 | 15.1 |
| *Klebsiella* spp. | 676 | 14.9 |
| *P. aeruginosa* | 597 | 13.2 |
| *E. coli* | 537 | 11.8 |
| *S. pneumoniae* | 378 | 8.3 |
| Other Enterobacterales | 349 | 7.7 |
| Intra-abdominal |  |  |
| *E. coli* | 1200 | 31.2 |
| *Enterococcus* spp. | 608 | 15.8 |
| *Klebsiella* spp. | 481 | 12.5 |
| *Bacteroides* spp. | 284 | 7.4 |
| Other Enterobacterales | 201 | 5.2 |
| *Candida* spp. | 194 | 5.0 |
| *P. aeruginosa* | 176 | 4.6 |
| Deep surgical site |  |  |
| *S. aureus* | 286 | 20.5 |
| *E. coli* | 236 | 16.9 |
| CNS | 154 | 11.0 |
| *Enterococcus* spp. | 146 | 10.4 |
| *Klebsiella* spp. | 124 | 8.9 |
| Skin and soft tissue |  |  |
| Gram-negative bacteria | 514 | 37.0 |
| *S. aureus* | 439 | 32.8 |
| *Enterococcus* spp. | 112 | 8.3 |
| *Streptococcus* spp. | 94 | 7.0 |
| HABSI: Hospital-wide includes hospital-acquired bloodstream infections. CNS: coagulase-negative staphylococci. | | |

**Appendix 6. Seasonal variation of pulmonary HABSI, by microorganism**

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*Monthly changes in incidence rate of pulmonary HABSI (2000–2014), stratified by infections associated with urinary catheterization (previous 7 days). Mixed-effects negative binomial regression analysis Random-effects: Hospital. Fixed-effects: year, month, university-affiliated hospital.*

Mixed-effects regression model of gram-negative pulmonary HABSI:

* Monthly peak-to-low (July-to-March) incidence rate ratio 1.70 (1.38–2.10, p<0.001)
* Seasonal peak-to-low (Spring-to-Summer) incidence rate ratio 1.25 (1.11–1.41, p<0.001)