Regional distribution of nosocomial infections due to ESBL-positive Enterobacteriaceae in Germany: data from the German National Reference Center for the Surveillance of Nosocomial Infections (KISS)

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Abstract

Surveillance systems for hospital infections are reporting increasing rates of extended-spectrum β-lactamase (ESBL)-positive Enterobacteriaceae in Europe. We aimed to perform a national survey on this trend and on the regional distribution of nosocomial infections due to ESBL-positive Enterobacteriaceae in German hospitals. Data from 2007 to 2012 from two components of the German national nosocomial infection surveillance system were used for this analysis. The data derive from intensive care units and surgical departments. Independent factors determining the proportion of ESBL-positive Enterobacteriaceae among nosocomial infections due to Enterobacteriaceae and changes in its regional distribution (broken down into German federal states) were calculated by regression analysis. From 2007 to 2012, the data showed a significantly increasing proportion of ESBL-positive Enterobacteriaceae in surgical site infections (from 11.46 to 15.38, 134%, p 0.003), urinary tract infections (9.36 to 16.56, 177%, p <0.001) and lower respiratory tract infections (11.91 to 14.70, 123%, p <0.001) due to Enterobacteriaceae. Factors independently associated with a growing proportion were: Thuringia (p 0.009; odds ratio (OR) 1.53), North Rhine-Westphalia (p <0.001; OR 1.41) and general surgery ward (p 0.002; OR 1.47). The proportion of ESBL-positive Enterobacteriaceae in nosocomial infections has significantly increased in Germany over the last 6 years. Hospitals in Central Germany and surgical departments in all of Germany are especially affected by this development.

Introduction

Third-generation cephalosporin resistance in Enterobacteriaceae is an important issue in hospital infections and intensive care [1,2]. In order to obtain a clinical view of the proportion of infections due to ESBL-positive Enterobacteriaceae (ESBL-E), we aimed to perform an over-time analysis on the proportion of ESBL resistance based on reported nosocomial infections associated with Enterobacteriaceae within the German national nosocomial infection surveillance system (KISS). KISS was established in 1997 following the example of the U.S. National Nosocomial Infections Surveillance (NNIS) system, initially focusing on intensive care unit (ITS-KISS) and postsurgery patients (OP-KISS). As in the NNIS system, KISS was set up with voluntary participation and confidential data feedback to participating units. Our analysis concentrates on data on nosocomial surgical site infections (OP-KISS) and nosocomial infections in intensive care units (ITS-KISS).

Methods

Data from two components of the German national nosocomial surveillance system (KISS) from the period from 2007 to 2012 were used for the analysis: data on nosocomial primary bloodstream infections and urinary tract infections from intensive care units (ICU) and OP-KISS data on surgical site infections (SSI) following a wide range of procedures from surgical departments. Nosocomial infections were determined

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following the definitions of the U.S. Centers for Disease Control and Prevention. Active prospective surveillance of SSI—including lower respiratory tract infection, urinary tract infection and bloodstream infection—is performed by trained staff. Detailed methods for OP-KISS [3] and ITS-KISS [4–6] have been previously described.

The proportion of ESBL-positive organisms among nosocomial infections due to Enterobacteriaceae was calculated by dividing the number of all nosocomial infections due to ESBL-producing Enterobacteriaceae by the number of all infections due to Enterobacteriaceae, multiplied by 100. A Cochrane-Armitage test was used as univariate trend analysis of the ESBL proportion among nosocomial infections due to Enterobacteriaceae between 2007 and 2012.

To assess the influence of different factors on the trend of the ESBL proportion among nosocomial Enterobacteriaceae infections, a multivariate logistic regression analysis was performed. The following variables were considered in the model by forward selection: year (2007 to 2012), sex, age (0–50, 51–65, 66–70, 71–120 years), type of hospital (university hospital, academic teaching hospital, other hospital), season, type of ICU or type of surgical department, and hospital size ($\leq$400 beds, >400 beds). Parameters were entered into the model at a significance level of $p < 0.05$ and were removed at $p > 0.06$.

To analyse differences in the geographical distribution of the proportion of ESBL, we analysed the hospitals' geographical location by federal state. The data set consisted of sets from 2011 and 2012. Further model parameters were the same as for the yearly trend analysis. To assess their individual influence separately, each parameter was binary coded (with reference = 0). Only the parameter of survey year was analysed as continuous parameter. Stepwise forward selection was used to derive a logistic regression model. Parameters were entered into the model at a significance level of $p \leq 0.05$ and were removed at $p > 0.05$.

All computations were performed by R 3.01 (R Foundation for Statistical Computing Vienna, Austria; mapping material: http://gadm.org) and SAS 9.3 (SAS Institute, Cary, NC).

Results

Of the existing 2017 hospitals in Germany in 2012, 645 ICUs with 9011 intensive care beds sent data to ITS-KISS and 681 surgical departments reported data to OP-KISS. From 2007 to 2012, we found an upward trend over time in the proportion of ESBL among the analysed nosocomial infections due to Enterobacteriaceae (Fig. 1). The univariate analysis showed a statistically significant upward trend among surgical site infections (p 0.003), urinary tract infections ($p < 0.001$) and lower respiratory tract infections ($p < 0.001$) due to *Escherichia coli* (Table 1).

In the regression analysis, the following factors were associated with a statistically significant impact on the proportion of ESBL between 2007 and 2012: surgical ICU (odds ratio (OR) 1.36), multidisciplinary ICU (OR 1.30) and hospital $\leq$400 beds (1.20). The parameter of year was significantly associated with the ESBL-E proportion (OR 1.07), which represents a yearly increase in the proportion of ESBL-E by 7%. Results are displayed in Table 2.

In the regression analysis for geographical distribution, the following factors were associated with a significantly increased proportion of nosocomial infection due to ESBL-E: the federal states of Thuringia (p 0.009; OR 1.53; 95% CI 1.11–2.09) and North Rhine-Westphalia ($p < 0.001$; OR 1.41; 95% confidence interval (CI) 1.17–1.69) and surgical ICU (p 0.002; OR 1.47, 95% CI 1.15–1.88). The geographical distribution from 2007 to 2012 in 2-year steps is shown in Fig. 2.

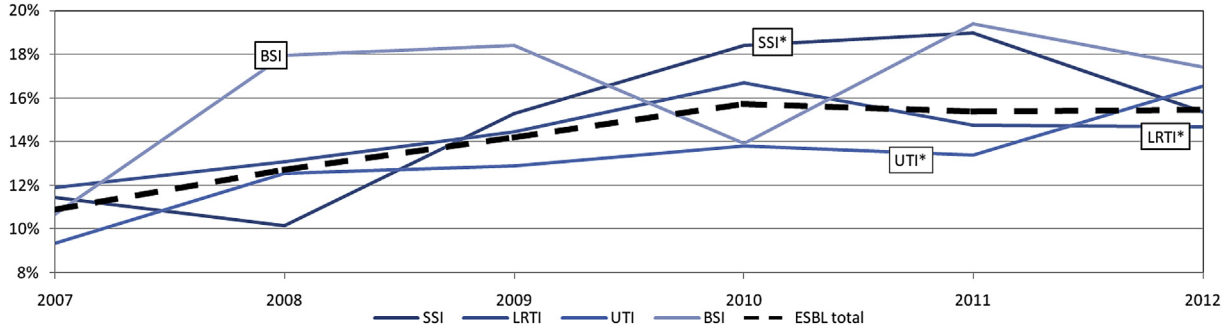

FIG. 1. Proportion of ESBL over time of nosocomial infections due to Enterobacteriaceae. *Statistically significant trend (Cochrane-Armitage test). ESBL, extended-spectrum β-lactamase; SSI, surgical site infection; LRTI, lower respiratory tract infection; UTI, urinary tract infection; BSI, bloodstream infection.

TABLE 1. Participating departments and intensive care units per 2-year period, nosocomial infections and results of univariate analysis for trend from 2007 to 2012 in ESBL proportion of nosocomial infections due to Enterobacteriaceae

	2007–2008		2009–2010		2011–2012		
Infection	**Overall**	**ESBL**	**Overall**	**ESBL**	**Overall**	**EBSL**	**p (Cochrane-Armitage test)**
Enterobacteriaceae infections	3951	469 (11.9%)	4542	681 (15.0%)	4409	680 (15.4%)	<0.001*
Escherichia coli	2579	279 (10.8%)	2991	449 (15.0%)	2826	494 (17.5%)	<0.001*
Klebsiella pneumoniae	1372	190 (13.8%)	1551	232 (15.0%)	1583	186 (11.7%)	0.091
OP-KISS							
No. of surgical departments	432		558		681		
Surgical site infection	593	64 (10.8%)	667	113 (16.9%)	681	118 (17.3%)	0.003*
E. coli	497	59 (11.9%)	557	103 (18.5)	550	107 (19.5%)	0.003*
K. pneumoniae	96	5 (5.2%)	110	10 (9.1%)	131	11 (8.4%)	0.584
ITS-KISS							
No. of intensive care units	465		533		645		
Lower respiratory tract infection	1768	221 (12.5%)	1945	303 (15.6%)	2241	330 (14.7%)	0.034*
E. coli	899	102 (11.3%)	1014	165 (16.3%)	1180	218 (18.5%)	<0.001*
K. pneumoniae	869	119 (13.7%)	931	138 (14.8%)	1061	112 (10.6%)	0.040*
Urinary tract infection	1389	154 (11.1%)	1690	226 (13.4%)	1226	184 (15.0%)	<0.001*
E. coli	1082	105 (9.7%)	1301	166 (12.8%)	969	142 (14.7%)	<0.001*
K. pneumoniae	307	49 (16.0%)	389	60 (15.4%)	257	42 (16.3%)	0.845
Bloodstream infection	201	30 (14.9%)	240	39 (16.3%)	261	48 (18.4%)	0.350
E. coli	101	13 (12.9%)	119	15 (12.6%)	127	27 (21.3%)	0.064
K. pneumoniae	100	17 (17.0%)	121	24 (19.8%)	134	21 (15.7%)	0.635

ESBL, extended-spectrum β-lactamase; KISS, German national nosocomial infection surveillance system; OP, surgical department; ITS, intensive care unit. *Indicates statistical significance.

TABLE 2. Independent factors for alteration of ESBL proportion of nosocomial infections due to Enterobacteriaceae between 2007 and 2012 from multivariate analysis

Parameter	**OR**	**95% CI**	**p**
Year	1.073	1.042; 1.105	<0.0001
Age >70 years	0.806	0.690; 0.940	0.0062
Surgical ICU	1.357	1.146; 1.608	0.0004
Gynecology	0.371	0.150; 0.916	0.0316
Interdisciplinary ICU	1.296	1.153; 1.457	<0.0001
ICU other	0.832	0.698; 0.990	0.0385
Hospital ≤400 beds	1.201	1.078; 1.338	0.0009
Spring	0.877	0.781; 0.984	0.0257

ESBL, extended-spectrum β-lactamase; OR, odds ratio; CI, confidence interval; ICU, intensive care unit.

Discussion

Rising infection rates due to ESBL-E have been observed internationally [7]. Our data confirm these numbers for the German hospitals participating in KISS and show a strong increase of nosocomial ESBL-E infection in the midwest of Germany. Interestingly, the lion's share of the German pork production is situated here (http://www.bmelv.de), and pork has been linked to colonization with ESBL-E [8,9]. In Germany, the majority of antibiotic consumption is found in agricultural production [10]. However, building a causal relationship towards rising rates of ESBL-positive organisms would oversimplify the complexity of the existing facts [11,12]. There are different ways of introduction and distribution of ESBL-positive organisms that are being currently discussed, including the food chain [11], selection pressure [10,13] and a concentration gradient based in states with high colonization rates [8,14]. The spread of ESBL-E is therefore likely to have a multifactorial cause.

Studies on risk factors for acquisition of ESBL-positive organisms demonstrate that antibiotic treatment or hospital stay [15,16] are important drivers. In Germany, 70% of single-shot surgical prophylaxis is administered longer than recommended [13]. The results at hand underline this assumption by showing an association with surgical ICUs. Our results also support the finding that infections due to gram-negative bacteria are less likely to occur in colder seasons [17]. Our data confirm several studies on infections due to ESBL-positive bacteria that show a trend towards infections in patients younger than 70 years old [18,19].

Our data did not derive from a random selection of German hospitals but represent a considerable portion: 34% (n = 9011) of the 26 162 existing ICU beds in 2012 are represented in our network (http://www.gbe-bund.de). We did not adjust for potential outbreak scenarios. The proportion found could therefore mirror casual outbreaks. However, the continuous trend of ESBL-positive infections over time argues against this interpretation. There is evidence that the larger part of hospital infections due to Enterobacteriaceae is community acquired [20]. Because our data is based on nosocomial infections, the interpretation can only be valid for this type of infection. Nosocomial infections are influenced by the hospital's ecological flora and are suspected to be selected under the hospital's antimicrobial pressure.

The proportion of ESBL-positive nosocomial infections in the last 6 years has significantly increased in Germany.

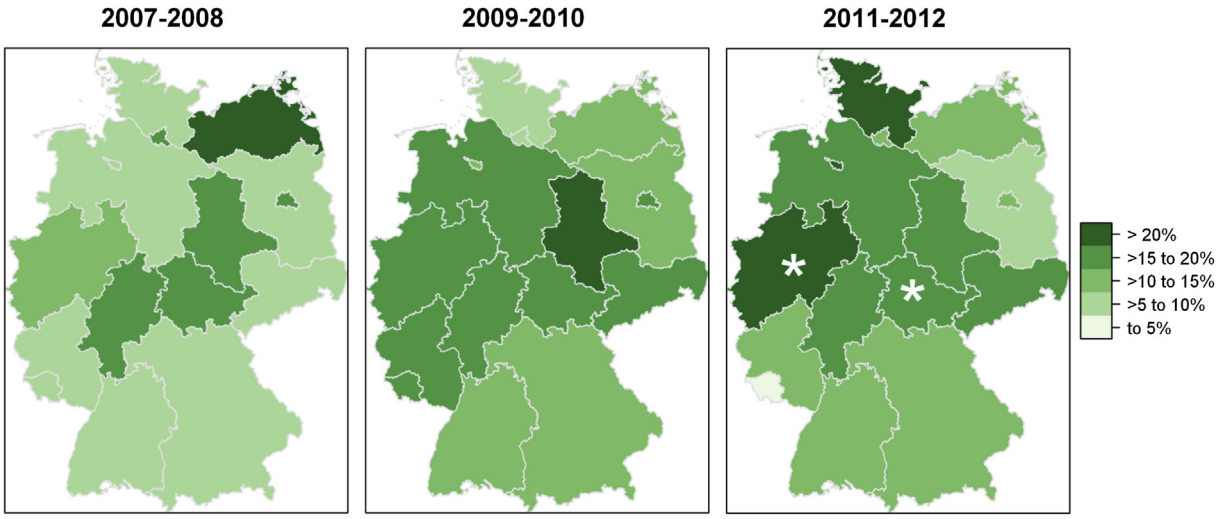

FIG. 2. Comparison of federal state–dependent proportion of ESBL in nosocomial infections due to Enterobacteriaceae from ITS-KISS and OP-KISS from 2007 to 2012. *Significantly increased proportion in ESBL in 2011 and 2012 compared to other regions (multivariate logistic regression analysis). ESBL, extended-spectrum β-lactamase; KISS, German national nosocomial infection surveillance system: ITS, intensive care unit; OP, postsurgery patients.

Hospitals in central Germany and surgical ICUs are particularly affected. It is important to implement and comply with effective prevention measures to avoid further spread of these organisms.

Transparency declaration

All authors report no conflicts of interest relevant to this article.

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