Dramatic increase in vancomycin-resistant enterococci in Germany

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Objectives: Among European countries, Germany has one of the highest proportions of vancomycin-resistant Enterococcus faecium bloodstream infections. The aim of this study was to investigate the development of vancomycin-resistant enterococci (VRE) in German hospitals and to consider the regional distribution of VRE in Germany.

Methods: Data from three components of the German national nosocomial surveillance system (KISS) from the period 2007–12 were used for analysis: ICU-KISS data on nosocomial primary bloodstream infections and urinary tract infections from intensive care units (ICUs); OP-KISS data on surgical site infections from surgical departments; and Pathogen-KISS data concentrating on VRE cases (infections and colonizations) in ICUs. Trends over time were calculated and a map according to German federal states was prepared.

Results: Data from up to 645 ICUs and 681 surgical departments for 2 year periods from 2007 to 2012 were analysed. The proportion of VRE increased significantly for surgical site infections (526%; P < 0.01) and bloodstream infections (265%; P < 0.01) and non-significantly for urinary tract infections (278%; P = 0.07). A large subgroup of ICUs also reported VRE cases in the same period, with a significant increase of 282%. The mapping of federal states showed large variation in VRE proportions and incidence rates in a belt of states with significantly higher VRE proportions from west (North Rhine-Westphalia) to east (Saxony).

Conclusions: The high overall VRE proportion in Germany is mainly due to the situation in four states. There is an urgent need to analyse the epidemiology of VRE in detail to develop appropriate infection control strategies.

Keywords: multiresistant, epidemiology, surveillance

Introduction

Enterococcus is the third most important bacterial genus causing nosocomial infections in Germany.1 Vancomycin-resistant enterococci (VRE) were first isolated in 1986 in Europe.2 Vancomycin resistance is independently associated with increased mortality among patients with enterococcal bloodstream infections.3,4

In the last century bloodstream infections with VRE were still rare in Germany.5 Increased VRE prevalence was first noted in south-western German hospitals in 2003 and marked by several outbreaks in hospitals in Baden-Württemberg.6

However, recent data from the European Antimicrobial Resistance Surveillance Network (EARS-Net) have highlighted that Germany has one of the highest proportions of vancomycin-resistant Enterococcus faecium in Europe, a proportion of 16.2% (data from 2012). Only Ireland (44.0%), Portugal (23.3%) and Greece (17.1%) have higher proportions of vancomycin-resistant E. faecium. Neighbouring countries have much lower vancomycin-resistant proportions (Denmark, 2.0%; the Netherlands, 0.0%; France, 0.8%; Belgium, 1.4%; Austria, 3.2%; and Poland, 8.4%).7

Vancomycin-resistant E. faecium proportions are even higher (in all materials, not only blood culture results) according to the data of the German Antimicrobial Resistance Surveillance (ARS) system of the Robert Koch Institute. This database describes an increase from 16.2% in 2008 to 18.5% in 2012 in hospital settings and from 9.3% in 2008 to 19.4% in 2012 in ambulatory settings.8

The aim of this article is therefore to investigate the development of VRE in the large number of hospitals participating in the German national nosocomial infection surveillance system (Krankenhaus-Infektions-Surveillance System; KISS) and to consider the regional distribution of VRE in order to get further insight into the epidemiology of VRE in Germany.

Methods

Data from three components of KISS from the period 2007–12 were used for analysis: (i) ICU-KISS data on nosocomial primary bloodstream infections and urinary tract infections from intensive care units (ICUs); (ii) OP-KISS data on surgical site infections following a wide range of
procedures from surgical departments; and (iii) Pathogen-KISS data concentrating on VRE cases (infections and colonizations) in ICUs.

The methods of the above-mentioned KISS surveillance components are described in detail elsewhere.9–11 The definitions of the CDC were used for all components.12 In three components, there is no distinction between E. faecium and Enterococcus faecalis; the term VRE therefore describes the proportion of VRE among all enterococcal infections. In Pathogen-KISS, VRE identified between days 1 and 3 are considered present at admission and VRE identified beginning on day 4 after admission to the ICU are considered ICU acquired.

Data from ICU-KISS and OP-KISS were combined and analysed separately (dataset 1). For dataset 1, the proportion of VRE isolates was calculated by dividing the number of resistant isolates by the number of all enterococcal isolates and multiplying by 100. For dataset 2, VRE incidence rates (VRE infections/colonizations per 100 admitted patients) were calculated.

Yearly trends in VRE proportions and differences between German federal states were analysed using logistic regression analysis. The dataset for yearly trend estimation contained data from 2007 to 2012, and every model included year as a variable (from 2007 to 2012). Possible additional parameters for entering into the model were gender, age (0–50, 51–65, 66–70 and 71–120 years), type of hospital (university hospital, academic teaching hospital and other hospital), season, type of ICU or type of surgical department, and hospital size (<400 beds and ≥400 beds). Dataset 2 was analysed with the Cochran–Armitage test for yearly trends.

The dataset for analysis of differences between German federal states included only data from 2011 to 2012. Possible model parameters were the same as used for the yearly trend analysis supplemented by the parameter federal state. For this analysis, each parameter was dummy coded to analyse its influence separately. 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 analyses were performed using R 3.01 (R Foundation for Statistical Computing Vienna, Austria; http://gadm.org) and SAS 9.3 (SAS Institute, Cary, NC, USA).

Results

Dataset 1: VRE proportions of nosocomial infections (%)

A large number of ICUs and surgical departments reported data about pathogens causing nosocomial infections in the period 2007–12 (Table 1). The proportion of VRE increased significantly from 0.87% to 4.58% for surgical site infections (526% increase, \( p < 0.001 \)) and from 4.91% to 12.99% for bloodstream infections (265% increase; \( p < 0.001 \)) and non-significantly from 2.23% to 6.19% for urinary tract infections (278% increase; \( p = 0.07 \)) in the period 2007–12 (Figure 1).

Dataset 2: incidence rates of VRE cases (per 100 admitted patients)

A large subgroup of the ICUs in Table 1 also reported VRE cases (infections and colonizations) in the period 2007–12 (Table 2). On average 7.5 VRE cases were observed per ICU per year during the period 2011–12.

Discussion

Both KISS datasets used for the analysis showed a significant increase in VRE in the period between 2007 and 2012 and therefore confirm both the EARS-Net data and the data from the German surveillance system for antibiotic use and bacterial resistance in ICUs (SARI), with an increase in vancomycin-resistant E. faecium from 2.3% to 11.4% (\( p < 0.001 \)) in the period from 2001 to 2011.13

The reasons for this increase are not clear and the belt of higher VRE rates in the middle of Germany is astonishing and difficult to explain.
explain. Other countries have also observed remarkable regional differences. French colleagues identified a focus in the north-western part of the country. 14 Canadian researchers found a higher incidence in the western part of the country. 15 Cattoir and Leclercq 16 recently observed that ‘despite considerable research, the reasons for the emergence and rapid spread of VRE remain obscure’, and Ziakas et al.17 described a trend for reduced VRE in US hospitals.

The occurrence of VRE in the environment has often been demonstrated. Many articles describe the identification of VRE in farm animals, such as pigs, 18,19 turkeys20 and chickens.21 The reason for VRE being present in farm animals may be selection by extensive use of the vancomycin analogue avoparcin for growth promotion.22,23 However, VRE has also been found in wild animals, e.g. rooks.24 Some authors have also described the occurrence of VRE in foods, e.g. cheese and meat.25,26 An association between VRE in animals, food and clinical samples has been seen by several authors.19,22,25,27 However, recent data from Willems et al.28 using Bayesian population genetic analysis showed a significant association of hospital (clonal complex 17) and farm animal isolates of \( E. faecium \) with different genetic groups. Therefore, there seems to be no association between the environment and the increased VRE rates in German ICUs and the differences between the various regions.

Secondly, VRE can also be acquired in hospitals by transmission from patient to patient.19,20 However, a relatively low hospital transmission rate was observed recently in a German university hospital on an endemic VRE level.21 In addition, the eastern federal states in the belt have the lowest MRSA rates in Germany (E. Meyer, C. Schröder, P. Gastmeier and C. Geffers, unpublished results). Therefore, a general increase in transmission rates and differences in transmission rates between federal states do not provide a satisfactory explanation.

Thirdly, the development of new VRE strain characteristics and spread in a specific area of Germany could also explain the increase in VRE. For instance, the same group of researchers mentioned above (i.e. Willems et al.28) identified a locus that encodes a putative phosphotransferase system (PTS) by using comparative genome analysis and subsequent PCR screening. The PTS locus was widespread in isolates from hospital outbreaks of infection (84.2%) and non-outbreak clinical infections (66.0%), but absent
from human commensal isolates. Several genomic regions were found to mainly recombine in specific hospital-associated E. faecium strains.

Finally, another hypothesis for this VRE increase and the regional differences could be a variation in antibiotic usage habits. No significant association of VRE incidence with vancomycin use was described for German ICUs. However, during investigations of VRE outbreaks in US hospitals it was noted that VRE isolation was only weakly associated with exposure to vancomycin. However, the reports indicated that VRE isolation was associated with exposure to extended-spectrum cephalosporins and agents with potent activity against anaerobic bacteria, presumably by reducing the number of competitive flora in the colon. In addition, anti-anaerobic agents appear to increase the output of VRE in the faeces. Unfortunately we have no data about antibiotic usage habits in the individual federal states. According to data from the recent German national prevalence study, the most frequently administered antibiotic groups were second-generation cephalosporins (14.6%) and fluoroquinolones (14%), followed by penicillins with β-lactamase inhibitors (12.6%) and third-generation cephalosporins (10.6%). Glycopeptides and metronidazole were not among the 10 most frequently used substances.

The use of both KISS datasets has limitations

Using proportions of VRE for all nosocomial enterococcal infections has the advantage that infections have the highest clinical impact and are not confounded by other changes over time, such as the frequency of microbiology reports. However, the overall number of nosocomial VRE infections is still relatively low, meaning that random effects should be considered when comparing the federal states.

The advantage of concentrating on the total number of VRE cases is a much higher number of cases, but this information may be biased by variation in screening habits. In addition, the clinical impact of considering colonized patients is lower. Unfortunately, our surveillance system only collects information about the number of VRE cases and we do not have any information about the distribution of certain VRE strains.

A further limitation is the lack of distinction between vancomycin-resistant E. faecium and vancomycin-resistant E. faecalis in both surveillance components. The proportion of vancomycin-resistant E. faecium is increasing and the proportion of E. faecalis is decreasing. In addition, only about half of the ICUs in Germany participate in ICU-KISS and about a quarter in Pathogen-KISS. Finally, no information about the distribution of VanA and VanB and further strain characteristics is available and neither is information about the occurrence of outbreaks in the ICUs.

Conclusions

Knowledge about the true epidemiology of multidrug-resistant pathogens is a prerequisite for the introduction of appropriate infection control measures. Until now the dramatic increase in VRE has not been recognized in Germany and the predominant ways in which VRE spread are still unknown. The strain characteristics of VRE in the four belt states (North Rhine-Westphalia, Hesse, Thuringia and Saxony) and the other regions should be analysed in detail and compared. It should be investigated further whether the use of antibiotics with anti-anaerobic potential has increased during recent years in Germany, perhaps in particular in the ‘belt states’. There is an urgent need to analyse the sources of this VRE increase in Germany in detail to help in the development of appropriate infection control strategies.

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Transparency declarations

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References


