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Outbreaks caused by vancomycin-resistant *Enterococcus faecium* in hematology and oncology departments: A systematic review

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Abstract

Background: Vancomycin-resistance in *Enterococcus faecium* (VRE) poses a major threat in health care settings. It is well known that patients in hematology and oncology departments are especially at risk of nosocomial VRE acquisition. This systematic review of the literature provides data on the main sources, transmission modes and potential risk factors for VRE acquisition as well as appropriate infection control measures in order to terminate such nosocomial outbreaks.

Methods: Data on nosocomial VRE outbreaks on hematology and oncology wards was retrieved from the Outbreak Database and PubMed.

Results: A total of 35 VRE outbreaks describing 757 affected patients and 77 deaths were included in this review. The most frequent site of pathogen detection were stool samples or rectal swabs (57% of all isolation sites), followed by blood cultures (30%). The most common outbreak source was an index patient. The main

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modes of transmission were 1) hands of health care workers, 2) contact to a contaminated environment and 3) patient-to-patient contact. The most common risk factor for VRE positivity was prior antibiotic treatment. The most common infection control measures performed were screening and isolating or cohorting of patients.

Conclusion: A rational use of antibiotics in hematology and oncology units is recommended in order to reduce selection pressure on resistant pathogens such as VRE. In addition the importance of hand hygiene should be stressed to all staff whenever possible.

Keywords: Infectious disease, Medicine, Internal medicine, Oncology

1. Introduction

Patients in hematology or oncology departments are considered to be the most severely immuno-compromised patient population and thus, outbreaks with multi-drug resistant organisms are of major concern in these departments. Enterococci are among the most frequently identified pathogens causing outbreaks in this particular group of patients (Ruhnke et al., 2014). In particular bloodstream infections (BSI) due to vancomycin-resistant *Enterococcus faecium* (VRE) are associated with substantial morbidity. Mortality of BSI almost doubles when caused by a VRE compared to BSI from Vancomycin-susceptible *E. faecium* (Prematunge et al., 2016).

There is uncertainty regarding the most effective infection control and prevention (ICP) measures in order to avoid endemic nosocomial VRE spread (Edmond et al., 2015; Morgan et al., 2015; Simon and Christiansen, 2012; Welsh, 2015). Unfortunately there is very little data available on this topic. A recently published meta-analysis including 4 interrupted time series, 3 controlled clinical trials and 1 cluster randomized clinical trial (De Angelis et al., 2014) found that hand hygiene was associated with a 47% decrease of VRE acquisition but contact precautions did not significantly reduce the VRE acquisition rate, despite isolation of VRE positive patients being still widely recommended (Lepelletier et al., 2015; Muto et al., 2003).

As soon as a nosocomial outbreak is noticed, all ICP measures in place are usually enforced and often a bundle of additional measures are introduced. However, this results in hardly being able to determine which of those numerous measures had the greatest impact on the termination of the outbreak. Furthermore the experiences from a single outbreak event cannot be generalized because they are strongly influenced by the local setting in which the outbreak took place.

This difficulty can be overcome by analyzing a large number of VRE outbreaks in hematology and oncology departments. Therefore, a systematic review was

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performed in order to get a better insight into the characteristics of VRE outbreaks. This information may be very useful when choosing certain ICP measures during an outbreak investigation.

2. Material and methods

2.1. Search strategy

The Outbreak Database (http://www.outbreak-database.com) is the world's largest collection on all kinds of nosocomial outbreaks (Vonberg et al., 2011). In this database all outbreaks are filed in a standardized manner. This way the user may perform a specific search combining outbreak parameters of interest. The following search strategy was applied on 29th of March 2017:

microorganisms = [vancomycin-resistant *Enterococcus faecium*] AND location = [hematology/oncology]

To identify additional articles which are not yet filed in the outbreak database, but also relevant to the topic of interest, two additional searches of PubMed were performed on the same day using the following combination of mesh terms:

[hematology] AND [vancomycin-resistant *Enterococcus faecium*]

[oncology] AND [vancomycin-resistant *Enterococcus faecium*]

Reference lists of all so-retrieved articles were then checked for further potentially relevant outbreak reports.

2.2. Inclusion criteria, extraction of data and statistics

VRE outbreaks from hematology and/or oncology patients were included in the analysis only if the exact number of affected patients was clearly stated in the outbreak report. There were no restrictions with respect to the type of article and the year of its publication.

Besides the number of patients involved, the following items from each VRE outbreak report got extracted if mentioned: a) year of publication, b) country, c) distribution of infections and colonisations, d) infection rate (= number of infected patients divided by the number of all VRE positive patients), e) mortality rate (= number of deceased patients divided by the number of infected patients), f) overall duration of the outbreak, g) source of the pathogen, h) mode of VRE transmission, i) risk factors for VRE acquisition and j) implemented infection control measures.

All statistical analyses including calculation of means, minimum and maximum values, standard deviations and Pearson correlation coefficients were performed using PASW Statistics 19 (SPSS Inc., Chicago, IL, USA). The significance level was set to $p = 0.05$.

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3. Results

3.1. Search results

The search strategy of the Outbreak Database and PubMed as described yielded a total of 105 articles, thereof 38 articles that seemed to be appropriate for inclusion at first glance according to the criteria as mentioned above. However, after full-text reading 3 more articles had to be excluded, two articles because they did not clearly distinguish between hematology/oncology patients and patients from other medical departments (Kurup et al., 2008) (Hwang et al., 1998) and one article because it described an endemic situation rather than an epidemic setting (Park et al., 2011). Thus, eventually 35 articles (Böröcz et al., 2005; Burnie et al., 2002; Chadwick et al., 1996; Chlebicki et al., 2006; Deplano et al., 2007; Edmond et al., 1995; Gambarotto et al., 2000; Hanna et al., 2001; Iosifidis et al., 2012; Kawalec et al., 2000; Kawalec et al., 2001; Kawalec et al., 2007; Knoll et al., 2005; Lavery et al., 1997; Lesens et al., 2006; Loeb et al., 1999; Marcade et al., 2014; McCarthy et al., 2000; Montecalvo et al., 1994; Nolan et al., 2009; Nourse et al., 1998; Oh et al., 2004; Ozorowski et al., 2009; Pendle et al., 2008; Rizkalla et al., 1997; Rubin et al., 1992; Sample et al., 2002; Schmidt-Hieber et al., 2007; Schuster et al., 1998; Singh-Naz et al., 1999; Timmers et al., 2002; Valdezate et al., 2012; Wardal et al., 2014; Worth et al., 2007; Yoo et al., 2005) were considered appropriate for inclusion for further analysis (Fig. 1).

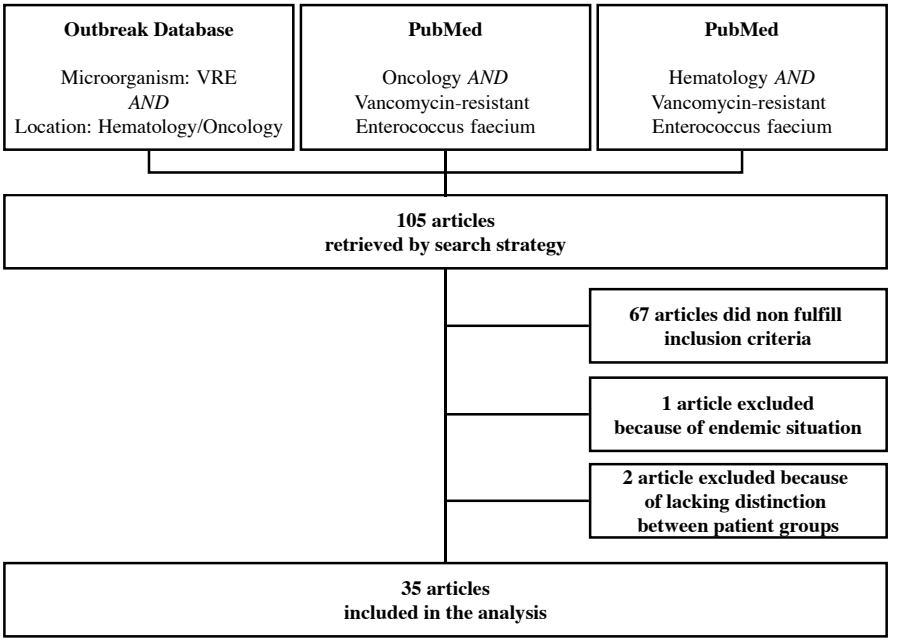

Fig. 1. PRISMA flow chart of literature search algorithm.

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3.2. Studies' characteristics, infections and mortality

There were 9 case control studies, 1 cohort study and 25 descriptive case series. All outbreaks were published between 1992 and 2014. The mean duration of a VRE outbreak was 11 months (range 1–36 months; Fig. 2). There was significant correlation ($r = 0.551$, $p < 0{,}01$) between the duration of the outbreak and the number of patients affected. Most outbreaks involved 10–19 patients; only 3 articles described VRE outbreaks involving >40 patients, thereof 1 outbreak reported by Kawalec et al. (2000) involved as many as 124 patients. The number of colonized and infected patients was missing in 10 articles. Twenty-five articles provided exact information about 468 VRE isolation sites (Table 1). VRE were most often found in stool samples, rectal swabs and/or perianal swabs (267; 56.9%) as well as blood cultures (141; 30%).

An overall infection rate ≥60% was reported from 6 VRE outbreaks compared to 6 other articles showing an infection rate ≤10%. A total of 757 patients were colonized or infected, thereof 101 patients developing BSI. There was data on 77 fatal cases presented in 17 articles (10.2% overall mortality rate).

3.3. Sources

In 9 articles an index patient was considered the source of the outbreak. Even though 14 outbreaks employed extensive environmental screening and 1 other article was unable to distinguish among various possible sources. There was not a single article that reported the environment being the definite outbreak's source. However, data on potential sources was completely missed out in 25 of the 35 (71%) outbreaks.

3.4. Modes of transmission

The transmission mode was addressed in 12 articles, of which three articles named more than one transmission mode. Six articles report patient-to-patient transmission.

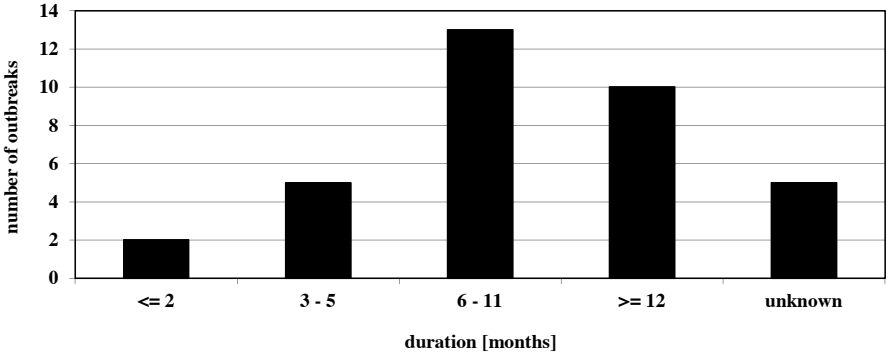

Fig. 2. Distribution of outbreaks according to duration.

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Table 1. Isolation sites of VRE.

Isolation site	Number (%)
stool, rectal swabs and perianal swabs	267 (57%)
blood cultures	141 (30%)
urine cultures	27 (6%)
lung and chest	20 (4%)
wound swabs	6 (1%)
sputum samples	5 (1%)
swabs from abdominal infections	1 (0.2%)
swabs from skin infections	1 (0.2%)
total	**468 (100%)**

In 5 cases transmission through the hands of health care workers was reported and in another 4 cases transmission was due to a contaminated environment.

3.5. Risk factors

By definition, risk factors can only be calculated from case-control studies (9 included) and cohort studies (1 included). Only 9 of those 10 articles did in fact provide such data from univariate or even multivariate analyses (Table 2) while the remaining study by Iosifidis (Iosifidis et al., 2012) did not present any risk factors at all.

3.6. Infection control measures

The number of ICP measures mentioned in VRE outbreak reports ranged from 1 to 9 (4.5 on average). The most frequently performed included the screening of patients (28 outbreaks), isolation and/or cohorting (21), enforced surface disinfection (15), and environmental screening (14) (Fig. 3). For further details please refer to the supplement.

A complete closure of the ward or unit was initiated in 6 VRE outbreaks. The duration of closure was as long as 5 weeks (Chlebicki et al., 2006) and even ranged up to 3 months (Iosifidis et al., 2012). There was no correlation between the amount of measures taken and the duration of the outbreak or the number of affected patients.

4. Discussion

4.1. Outbreak duration

With an average duration of 11 months VRE outbreaks in hematology and oncology departments show an extraordinary long course compared to nosocomial

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Table 2. Univariate and multivariate risk factors for acquisition of Vancomycin-resistant *Enterococcus faecium* in nosocomial outbreaks.

Article	risk factors in univariate analysis	risk factors in multivariate analysis
Nolan et al. (2009)		* enteral feeding tube, gastrostomy tube or nasogastric tube
		* lack of empirical contact precautions
Lesens et al. (2006)		* urinary catheter
		* prior exposure to third-generation cephalosporins
		* prior exposure to substances with anti-anaerobe activity
Worth et al. (2007)		* acute myeloid leukemia
		* vancomycin therapy during the previous 30 days
Timmers et al. (2002)		* antibiotic use within 1 month before admission
		* low albumin levels at baseline
Loeb et al. (1999)		* cephalosporin use
Singh-Naz et al. (1999)	* use of invasive devices	* young age
	* malignancy or sickle cell disease	* antimicrobial therapy
		* immunosuppression
Oh et al. (2004)	* length of hospital stay	
	* male gender	
	* care in a 6-bed room	
	* more surgical, vancomycin or ceftizoxime therapy	
	* less metronidazole therapy	
Edmond et al. (1995)	* gastrointestinal colonization with VRE	
	* exposure to metronidazole, clindamycin or imipenem	
Rubin et al. (1992)	* administration of antibiotics	
	* administration of vancomycin	
	* length of hospital stay	

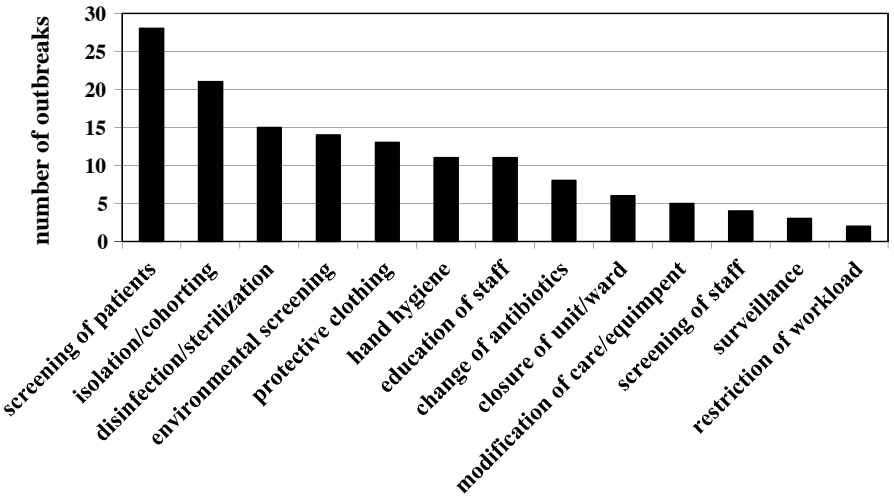

Fig. 3. Distribution of infection control measures.

outbreaks caused by other pathogens or by VRE in other patient populations (Satilmis et al., 2016; Sood and Perl, 2016; Stapleton et al., 2016). Several factors may contribute to this observation. First, enterococci present with a rather high tenacity and may survive even on dry inanimate surfaces for as long as several months (Kramer et al., 2006). Second, early detection of a resistant strain may be difficult because antibiotic susceptibility testing will not necessarily be performed if a common species from the physiological human gut flora (*E. faecium*) is identified. Third, although gradually increasing, the pathogenicity and virulence of enterococci is still rather low at present (Guzman Prieto et al., 2016; Van Tyne and Gilmore, 2014). Thus, the proportion of clinical samples in the routine diagnostic will also be quite low and active screening cultures need to be done in order to detect additional unknown carriers instead.

Awareness by staff on the ward as well as in the microbiological laboratory of the existence of VRE and their potential inter-patient spread is therefore strongly recommended. This way, VRE positive patients can be noticed early on, hopefully before transmission of the pathogen has occurred.

4.2. Isolation precautions, hand hygiene and environmental cleaning

Isolation or cohorting of VRE positive patients (colonized or infected) is recommended for infection control purpose (Ho et al., 2013; Mutters et al., 2013; Siegel et al., 2007) and this measure was in fact reported in about two thirds of all VRE outbreaks analyzed. One may speculate that isolation precautions were also implemented in at least some of the remaining outbreaks but the authors only failed to mention this detail in their article.

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A similar phenomenon may apply with respect to hand hygiene. Timmers et al. (2002) have clearly shown that VRE transmission can occur via the hands of health care workers which illustrates the importance of proper hand hygiene as a well-known corner stone of infection control (Reyes et al., 2016). However, for some unknown reason the enforcement of this basic ICP measure was mentioned in 11 articles only. This might be due to a general underreporting of enforced hand hygiene as an infection control measure, despite its use during an outbreak

Finally, intensified disinfection in near-patient areas is also recommended when a VRE outbreak is suspected (Mutters et al., 2013) due to the prolonged persistence of enterococci in the environment (Bradley and Fraise, 1996). Environmental contamination was in fact found as a potential source for VRE transmission in this systematic review in an outbreak report by Park et al. (2011), but only 15 out of 35 (43%) articles reported checking for and improving their current environmental disinfection practice. In our view special emphasis should be placed on toilet facilities and bed pans as they can easily get highly contaminated by VRE and other gastrointestinal pathogens (Eckstein et al., 2007; Goodman et al., 2008). This way, shared bathrooms may play an important role in pathogen spread via contamination of the environment. They may also facilitate direct patient-to-patient transmission via contaminated hands of patients after using the bathroom.

Unfortunately, even these days many outbreak reports are still not in accordance with the Outbreak Reports and Intervention Studies Of Nosocomial infection (ORION) Statement (Stone et al., 2007). As a consequence, there is often a lack of important information on ICP measures and other characteristics in outbreak reports including VRE outbreaks (Satilmis et al., 2016). We herewith recommend a stronger adherence to the ORION check list in the process of submission and during the review process.

4.3. Risk factors

Knowledge about specific risk factors is crucial when dealing with nosocomial infections and may help in preventing pathogen transmission. Prior antibiotic therapy was the most often stated multivariate risk factor for VRE positivity followed by the overall health status of the patient and the usage of invasive medical devices. Several studies have shown that the use of vancomycin affects the VRE selection rate (de Bruin and Riley, 2007). However antibiotics other than vancomycin may also be important in this context. Carmeli et al. (2002) conducted a matched case-control study to compare the influence of prior antibiotic usage on VRE emergence. They showed that the application of third generation cephalosporins, metronidazole and fluorquinolones may lead to an increased VRE rate in hospitals. Correa et al. (2015) conducted a study on risk factors for the emergence and spread of VRE in two hospitals in inner Brazil. Besides mechanical

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ventilation, the use of broad-spectrum antimicrobials was determined as the main risk factor for VRE acquisition.

The findings of this systematic review and the confirming findings of others emphasizes the importance of a rational use of all kinds of antimicrobial substances ("antibiotic stewardship") as an effective measure to also reduce the burden of VRE (Rubinstein and Keynan, 2013).

4.4. Decolonization

The effect on external VRE decolonization by daily bathing using chlorhexidine solution compared to bathing with routine soap was evaluated by Climo et al. (2009) in a quasi-experimental multicenter trial. When changing the regime from soap to chlorhexidine the VRE rate dropped by 50% (4.4 vs. 2.2 cases per 1,000 patient days; $p < 0.01$). Most probably as a consequence the incidence rate of VRE bacteremia also dropped significantly by 78% (3.38 vs. 0.74; $p = 0 > 0.05$). Kim et al. also found a 40% reduction of VRE BSI in a meta-analysis on the effectiveness of daily chlorhexidine gluconate bathing (Kim et al., 2016).

However, none of the outbreak reports included in our analysis mentioned "decolonisation" of any kind as an ICP measure to terminate VRE spread. We assume that this is due to the fact that all outbreaks in our systematic review were published before 2015 while chlorhexidine body-washing represents a rather new method for this purpose (Derde et al., 2014; Kim et al., 2016).

4.5. Blood stream infections

Most of the VRE isolates were grown from stool samples or rectal swabs (Table 1). This is less surprising considering the physiological habitat of *E. faecium* and the location for screening cultures. Positive blood cultures represented the second most common site of VRE isolation in our analysis of outbreaks from hematology and oncology departments (141 of 469; 30%). This is of particular importance considering the enormous clinical impact of BSI caused by VRE (DiazGranados et al., 2005). VRE bacteremia is often considered to be a breakthrough phenomenon from the colonized gut. Hefazi et al. could show that during the first 30 days after an allogeneic hematopoietic cell transplantation, 11% of the VRE colonized patients developed VRE BSI compared to only 5% in non-colonized patients (Hefazi et al., 2016). Similar results are reported by Rosko et al. from patients with hematologic malignancies but without undergoing stem cell transplantation (Rosko et al., 2014). So the avoidance of VRE spread by applying appropriate ICP measures will consequently reduce the number of infections and fatal cases.

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4.6. Limitations

There are always some limitations that have to be kept in mind when performing systematic reviews.

Publication bias may occur. There could be other VRE outbreaks that were not found and thus not included in our analysis for several reasons: Some outbreaks are just overseen by clinicians, some other outbreaks may not get published and some publications may be missed by the search strategy applied as described above.

Generalization of findings should be done with caution. Differences in the geographical setting and the time frame of investigated outbreak reports should always be taken into account. Furthermore, the results from VRE outbreaks on hematology and oncology units may not reflect the setting of other types of wards. For example the prevalence and the clinical outcome of VRE infections may significantly differ depending on underlying diseases and the type of medical department in charge (Chiang et al., 2017).

A single most important ICP measure cannot be determined. However, one may deduce from the results of this review that prior antimicrobial treatment is the most likely predisposition for VRE colonization. VRE colonization may than lead to VRE infection with BSI being the predominant type of infection.

Finally there is a lack of data in a large number of reports as mentioned above. Sometimes even basic information on the outbreak event is missing such as the number of infected and deceased patients. One would assume that this data were assessed during the outbreak investigation but for some reason did not get published in the article. Awareness of and better adherence to the ORION Statement (Stone et al., 2007) would therefore be much appreciated.

Declarations

Author contribution statement

Nikos Ulrich: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Petra Gastmeier: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Ralf Vonberg: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Competing interest statement

The authors declare no conflict of interest.

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