REVIEW ARTICLE

Control of the Spread of Vancomycin-Resistant Enterococci in Hospitals

Epidemiology and Clinical Relevance

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SUMMARY

Background: The spread of vancomycin-resistant enterococci (VRE), particularly *E. faecium*, in hospitals leads to many cases of colonization, but only sporadic infections. Detailed and valid risk assessment is needed so that patients at risk can be protected from VRE infection. The principal aims of risk assessment must include not only lowering VRE-associated morbidity and mortality in patients at risk, but also refraining from unnecessary anti-infective measures among those who are not at risk.

Methods: We selectively searched the PubMed database for pertinent articles on the epidemiology and clinical relevance of VRE in order to derive a uniform and practical hygiene strategy from the available scientific evidence.

Results: Only low-level evidence is available for the interventions studied to date, and most of the recommendations that have been issued can be characterized as expert opinion. As a rule, VRE are not highly pathogenic; they tend to have high rates of colonization, but low rates of infection. The risk factors for colonization with VRE include (among others) the administration of antibiotics and immunosuppressants, prior hospitalization, diarrhea, intubation, and other invasive treatments. The areas of highest risk are hematology/oncology wards, liver transplantation wards, dialysis units, and neonatology wards.

Conclusion: The chain of infection can be broken by improved and consistently applied standard hygienic measures (hand and surface disinfection). Some patients are nonetheless at elevated risk of VRE infection. In specific clinical situations, the optimal protection of these patients against VRE infection demands the obligatory enforcement of stricter hygienic measures (contact isolation).

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Enterococci are gram-positive, facultative anaerobic chain cocci with extremely high environmental resistance (1). Enterococci are known to cause, among other things, urinary tract infections, neonatal infections, and endocarditis (2). However, enterococci are generally not very virulent and are mostly found as colonization microbes in the intestine (2, 3). In fact, colonization occurs much more frequently than infections in hospitals (4).

Reports of enterococci resistance to glycopeptide antibiotics (such as vancomycin and teicoplanin) are increasingly frequent, and this is significant both therapeutically and epidemiologically. Distinctions can be made between a non-transferable natural resistance (VanC) and an acquired, transferable resistance, of which VanA and VanB are the most clinically relevant. VanA- and VanB-types of vancomycin-resistant enterococci (VRE) have similar microbiological behavior. However, achieving a microbiological diagnosis for the VanB genotype can be problematic, since VanB positive VRE often appear phenotypically vancomycin susceptible and the VanB resistance gene is prevalent in human intestinal commensals (5). Microbiologically, VanB-type VRE can be distinguished from the VanA-type VRE as it remains susceptible to teicoplanin. However, it has not yet been scientifically tested whether treating with teicoplanin could be a successful option.

Spread of vancomycin resistance

VRE first appeared in the late 1970s (6, 7) and is now spread worldwide (2, 8). In Germany, vancomycin resistance is almost exclusively restricted to strains of *E. faecium* (>99% of all VRE are *E. faecium*) (9, 10). Vancomycin-resistant *E. faecalis* are very rare (<1% of all *E. faecalis*) (10). Hence, despite differences in their pathogenicity, the two species are grouped together as VRE. There has been a trend towards an increase in vancomycin resistance in isolated *E. faecium* in recent years; it currently lies between 8% and 11% (10–13).

Epidemiology

Recent surveillance data from German hospitals (comprising a total of >10 000 beds) in the period of 2009 to 2010 show large regional differences in VRE

TABLE 1

Number of patients with VRE isolates in blood cultures in hospitals without general VRE screening

Year	Hospital A *1		Hospital B *1	
2010	4/357 470	(0.01)	8/346 603	(0.02)
2011	12/345 992	(0.04)	15/301 453	(0.05)
2012	2/230 250*2	(0.01)	5/173 633*3	(0.03)

*1 Number of cases/patient days (cases/1000 patient days); *2 01.01.2012–31.08.2012;
*3 01.01.2012–30.06.2012
VRE, vancomycin-resistant enterococci

TABLE 2

VRE-specific hygienic precautions in hospitals

Stage	Measures
I – (extended) standard precautions	– housing in multi-bed rooms – consistent hand disinfection – specific standard surface disinfection (following the list from VAH) – wipe disinfection of near-patient objects – disinfectant in bathrooms and washrooms – information signs for hand hygiene/wipe disinfectant after toilet use – use patient-dedicated equipment – patient-dedicated gown and glove precautions: – through direct patient contact – through contact with infectious material
II – contact isolation precautions	stage I, plus – organizational isolation (bed isolation and/or gown precautions, also for neighboring patients!) or – spatial isolation (single room or cohort isolation)

VRE, vancomycin-resistant enterococci;
VAH, Association for Applied Hygiene (Verbund für angewandte Hygiene)

prevalence. During this time, the incidence density (number of cases/1000 patient days) was 0.15–0.19, which is lower than the average values from German intensive care units (0.29 cases/1000 patient days) (14). Furthermore, these cases were usually colonization rather than infection.

VRE strains in a hospital setting are different from isolates in an outpatient setting and are referred to as hospital-associated strains. These are distinguished from commensal strains by molecular strain typing methods such multi-locus sequence typing (MLST) and multi-locus variance-analysis (MLVA) (2). The innovative combination of mass spectrometry and bioinformatics could represent an additional possible method for typing (15). However, detection of marker genes *(esp; hyl)* does not allow conclusions to be drawn about pathogenicity. Hospital strains display an arsenal of determinants, the expression of which could favor their tenacity and efficiency in colonization and even infection (16).

In contrast to methicillin-resistant *Staphylococcus aureus* (MRSA), there are no decolonization strategies for VRE, as the entire gastrointestinal tract can act as a reservoir, and successful decolonization is unlikely. Sufficient data is not available about the duration of colonization or the rate of possible recolonization. However, there are indications that at least some patients have been colonized over the long term or over long periods (17, 18).

Clinical relevance

The presence of VRE on microbiological examination of sample material often indicates colonization (19). It only rarely indicates the presence of an infection, such as for example when it is detected in blood cultures. However, there are certain groups of patients for whom the risk of infection by VRE is clinically particularly relevant. Additionally, clinical problems with VRE in the so-called risk areas of hospitals, i.e., those that house patients with an increased risk of infection, are rising in European hospitals. Infections with VRE also can result in longer inpatient stays and higher costs compared with those with nonresistant Enterococci (20). At-risk patients include neutropenic patients (odds ratio [OR] 12.46, 95% confidence interval [CI]: 1.53–101.21, p = 0.018), and in particular patients from hematology and oncology (OR: 7.96, 95% CI: 1.61–39.37, p = 0.011). In these patients, the risk of becoming infected with VRE has significantly increased (21, 22). Likewise, the risk of mortality due to VRE bacteremia is significantly higher than due to vancomycin-sensitive enterococci (VSE) bacteremia (OR: 2.52, 95% CI: 1.9– 3.4) (21, 23).

Similar to patients with neutropenia, or from hematology or oncology, liver transplant patients with VRE colonization have increased risks, both of infection (adjusted OR: 3.61, 95% CI: 2.01– 6.47) and death (adjusted OR: 2.12, 95% CI: 1.27– 3.54) (24, 25).

Other risk areas include neonatal intensive care units. However, available data for this are inadequate,

TABLE 3

Hygiene management for vancomycin-resistant enterococci in hospitals

	Stage I Standard precautions (general wards and outpatient units)	Stage II Contact isolation (at-risk patients *1 and risk areas *2,*3)
Spatial or organizational isolation (bed isolation)	–	+
Glove and coat precautions if direct contact with infectious materials	+	+
Mouth and nose protection if direct contact	–	–
Decolonization	–	–

*1 at-risk patients = infected patients, patients with secreting wounds, colonized patients with diarrhea, *C difficile*–associated diarrhea, stool incontinence, colonized patients with deficient personal hygiene

*2 risk areas = intensive care units, intermediate care units (monitoring units), hematology/oncology units (immunosuppressed patients in risk groups 2 and 3; transplantation units/ room), liver transplantation units and ICU/IMC with a high percentage of visceral surgical or gastroenterological patients; neonatology units and dialysis stations; ICU, intensive care unit, IMC, intermediate care;

*3 during VRE outbreak, also recommended for general wards.

\+ recommended

− not recommended /decolonization not possible

and individual studies have shown no significantly increased risk of infection for these departments (26, 27). As VSE have been described as pathogens in neonatal units, the risk in this vulnerable patient population of acquiring this difficult-to-treat infection should not be underestimated (2).

For chronic hemodialysis patients, it is questionable whether VRE detection is clinically relevant. Although these patients have high colonization rates, they do not seem to have either higher infection or mortality rates (28–30). However, there is evidence that some VRE strains are endemic to the renal area (e1).

In epidemiological studies, and in particular cohort and case–control studies, certain risk factors for VRE colonization have been identified. First and foremost is the administration of antibiotics, with a 1.25- to 31.9-fold increased risk (22, 24, 29–32). Additional factors include:

- previous hospitalization (3.7- to 39.8-fold increased risk) (28, 30, 32)
- diarrhea (48-fold increased risk) (33)
- administration of immunosuppressants (2.9-fold increased risk) (31)
- intubation, mechanical ventilation, and other invasive procedures (5.2- to 16.8-fold increased risk) (24, 31, 33)
- required chronic hemodialysis (3.9- to 5.8-fold increased risk) (28–30).

The picture is more heterogeneous when mortality is compared between VSE and VRE infections. Although some studies have shown that VRE bacteremia is associated with a significantly higher risk for mortality than VSE bacteremia (adjusted OR: 2.12, 95% CI: 1.27–3.54) (23), these observations could not be consistently reproduced. In a large retrospective cohort study, Haas et al. did not find significantly increased mortality (adjusted OR: 1.94, 95% CI: 0.78–4.8, p = 0.17) (31).

This heterogeneity could be due to the fact that VRE infection often has a polymicrobial etiology, and that not every case of VRE bacteraemia is clinically manifest (accompanied by symptoms of sepsis). It is possible that many cases of VRE bacteremia are only transient, clinically irrelevant bacteremia in multimorbid patients who have undergone many invasive procedures, because enterococci rarely cause severe systemic infection in people who are not severely immunosuppressed. In certain cases, however, there is an increased risk of infection, such as for patients with previously damaged heart valves (OR: 1.3, 95% CI: 0.8–20, p = 0.02) or liver transplant (OR: 7.2; 95% CI: 1.5–33.3; p = 0.01), or for patients undergoing hemodialysis (OR: 11.7, 95% CI: 1.1–122; p = 0.02) (34). A VRE infection is a serious disease for these patients and presents the physician with a major challenge, although even here new antimicrobials are effective (35). Nonetheless, successful treatment is not always guaranteed, and data for this are still lacking (36).

A number of strategies aimed at preventing the transmission of VRE, such as an active surveillance or contact isolation of VRE patients, have been investigated (37). However, these studies are often difficult to interpret because they were conducted during outbreaks (38), multiple interventions were implemented simultaneously (37), or relevant variables and possible sources of a statistical bias were not considered sufficiently (37, 39). Nonetheless, it is clear that the following situations or factors can lead to an increased risk of transmission:

- VRE outbreaks—due to unidentified deficiencies in hygiene management
- an increased proliferation potential of the causal VRE strain
- the presence of VRE infections, particularly in large-scale, secreting wounds (e.g., severe burn injuries)
- a higher risk of contamination of the environment in colonized patients (also enterostomata, etc.) who have diarrhea or stool incontinence
- poor compliance with hygienic measures, for a variety of reasons, in VRE-colonized patients.

TABLE 4

VRE risk areas and at-risk patients in hospitals

Risk areas	VRE at-risk patients
hematology/oncology units (immunosuppressed patients in risk groups 2 *1 and 3 *2; transplantation unit/room)	VRE infection, especially with secreting wounds (e.g., severe burn injuries and amputation)
liver transplantation units and ICU/IMC with a high percentage of visceral surgical or gastroenterological patients	VRE colonization with diarrhea, *C difficile* infection, stool incontinence (also enterostomata, etc.)
dialysis stations	VRE colonized patients with inadequate compliance

*1 risk group 2: severe immuonsuppression/immunodeficiency; *2 risk group 3: extremely severe immunosuppression/immunodeficiency; VRE, vancomycin-resistant enterococci; ICU, intensive care unit; IMC, intermediate care

Control of VRE in a hospital setting

Since large, controlled prospective studies that could provide data necessary to access further factors are still lacking, the following recommendations should be considered as our collective expert opinion. Hygiene recommendations for VRE must be practical, effective, and feasible, and should take into account current infection epidemiological findings. This is the only way that patients can be guaranteed effective care and safety despite limited resources. Several studies have already shown that bed occupancy rates and staffing have a direct impact on the incidence of nosocomial infections (40). A more rational use of limited hospital resources, both human and financial, is therefore mandatory. Earlier proposals and consensus recommendations should therefore be critically examined in this light (e2–e4).

Microbiological screening

Currently available data are insufficient to make an informed recommendation for VRE screening. Still, observations from various studies (13) suggest that, especially in comparison to MRSA and multidrug-resistant gram-negative bacteria (MRGN), VRE should be considered of lesser importance. For instance, two university hospitals without a general VRE screening reported that there was no increase of VRE detection in blood cultures (which can be used as a surrogate marker for invasive infections) (*Table 1*). The question of whether active VRE screening is useful depends on, among other things:

- the local prevalence at each hospital
- the sensitivity and specificity of the tests used
- internal conditions, such as limitations on the costs of screening.

Accordingly, and considering that each hospital can have different screening tests and a different local prevalence, no general threshold can be given to determine when VRE screening would be useful. There is evidence that risk-based screening of certain patients, similar as for MRSA, could identify most of the colonized patients (28, e5).

Generally, in the context of a VRE screening, swabs from wounds (especially deep abdominal wounds) and rectal areas and/or swabs from *Enterostomata* should be taken.

Extended VRE screening can be useful during outbreaks and periods of higher transmission risk to determine the extent of transmission and its possible routes, depending on the local conditions (for example, in specific risk areas). Similarly, routine VRE screening might be necessary in high-risk populations. The potential benefits of implementing general screening of high-risk cohorts depends on local prevalence at each hospital. In order to monitor and prevent outbreaks due to new, and possibly more virulent, strains of VRE, a monitoring center should be established. This center could carry out VRE prevalence studies at least once per year to capture trends in development. As a priority goal, the monotoring center has to place the focus on clinically relevant VRE problems, that is, the emergence of the pathogen in clinical specimens such as blood cultures and urine. Such a sentinel station could be established by the departments of the high-risk areas (21, 22, 24, 25, 28, 29). In addition, passive surveillance of positive VRE isolates from blood cultures remains an important tool to assess morbidity from severe VRE infections.

Hygiene management

Various studies have shown that hygiene and routine surveillance are effective in controlling VRE in endemic areas (33, e6–e12). Evidence-based precautions should be used especially at times when hospital resources are limited. Additional precautions may be necessary, in addition to consistent standard hygiene to protect vulnerable patients from infection. These can also successfully reduce VRE infections and, subsequently, lead to a decline in VRE incidence rates (e13). Nonetheless, use of resources must be considered, especially in the light of increasing problems with MRGN. The economic and care costs of resource intensive isolation measures for VRE should be critically assessed given the low infection rates (19). Additionally, isolation in single-person rooms negatively effects both the patient and the quality of care. Finally, being labeled as a VRE carrier is stigmatizing, and the social-psychological impact of this on patients has been hardly studied. However, isolation and stigmatization have already been demonstrated to have clear negative effects for patients with MRSA (e14–e16). Thus, isolation in a single room for the sole purpose of protecting other patients should only be done based on strict indications.

Both a valid risk assessment and prioritization are needed when dealing with multi-resistant pathogens to guide decision making about single-room isolation of patients colonised with VRE. A high level of adherence to hand hygiene protocols prevents the spread of all pathogens, regardless of whether the carrier status is

known. For this reason, some institutions implement only simple measures such as standard hygiene precautions (Haefner H, et al.: Results of a 3 month universal vancomycin-resistant enterococci screening of patients of an intensive care unit (ICU). DGHM; Essen, Germany 2011). The most important measure for control of VRE remains standard hygienic precautions (e3). In addition, using disposable gowns and gloves is advised for near-patient activities and should be mandatory when handling infected body parts or secretions. This is also recommended when patient-related care equipment (such as stethoscopes and blood pressure cuffs) are used, regardless of VRE status.

Recommendations

In the following recommendations, we will distinguish between (extended) standard hygiene precautions (stage I) and isolation precautions (stage II) (for details, see *Table 2*).

In VRE-colonized, non-risk patients in general wards, strict compliance with standard hygiene (stage I) is sufficient. Due to the increased tenacity of VRE on inanimate surfaces, consistent and regular surface disinfection of near-patient areas is an important measure for transmission prevention.

Organizational isolation (bed space isolation and/or glove and gown precautions) or spatial isolation (single room or cohort isolation) as per stage II should be implemented only during outbreaks (*Table 3*).

Where organizational isolation is indicated, glove and gown precautions should be used even for non-colonized neighboring patients. This not only avoids triggering anxiety in adjacent beds because of the stigma of the patient as transmitter but also increases awareness, and thus compliance, by physicians and nurses.

During outbreaks or increasing rates of VRE, the basic hygiene of staff and the implementation of surface disinfection should be critically reviewed. Due to their high tenacity, VRE can be transmitted if there is inadequate surface disinfection of the inanimate environment.

To reduce possible contamination through the environment, it is important to provide a disinfectant in the bathrooms and washrooms, and to install information signs that describe proper hand hygiene for VRE-colonized patients before and after using the toilet. After each toilet use, patients themselves should disinfect by wiping (for example, the toilet rim) (*Table 2*). In this case of large-scale contamination, this should be done specifically by the staff.

Hygiene management in risk areas should be assessed differently as compared to normal areas. The following major areas of risk for VRE have been identified in the literature (*Table 4*):

- hematology/oncology units (immunosuppressed patients in risk groups 2 and 3; transplantation unit/room)
- liver transplantation units
- dialysis stations
- neonatology (especially neonatal intensive care units [NICU]).

VRE-colonized patients in these areas should be treated strictly according to stage II (*Table 2*); that is, there should be an organizational or a spatial isolation. It should be taken into account that there is a potential increase of risk in these areas both of self-infection by VRE colonized patients and of transmission (and thus outbreak). In addition to the aforementioned risk areas, specific individual patients have increased risks of transmitting or acquiring VRE (*Table 4*).

These patients should be put into contact isolation according to stage II, even if they are outside these risk areas. If transmission is suspected, typing may help to uncover the epidemiological contexts.

Conclusion

Vancomycin-resistant enterococci have low pathogenicity in general. Usually, transmission of VRE (especially of *E. faecium*) causes a large number of colonizations but only sporadic infections. The chain of infection can be interrupted by implementing consistent and improved standard hygiene (such as hand and surface disinfection). However, at-risk patients have an increased risk of VRE infection. In certain clinical situations, optimal protection against infection for at-risk patients can be provided by strictly complying with strict hygienic precautions (contact isolation). The primary objectives must be to not only effectively reduce the VRE-related morbidity, mortality, and prolonged hospital stay for at-risk patients, but also to reduce precautions that are unnecessary for preventing infection in non-compromised patients.

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Conflict of interest statement

The authors declare that no conflict of interest exists.

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KEY MESSAGES

- Vancomycin resistance in enterococci in Germany is almost entirely limited to *Enterococcus faecium* (>99% of vancomycin-resistant enterococci [VRE]).
- Vancomycin-resistant enterococci usually have a low pathogenicity (characterized by high colonization and low infection rates).
- However, certain patient groups (neutropenic and neonatal patients, as well as those following liver transplantation or dialysis) have an increased risk of infection.
- The chain of infection can be disrupted by consistently implementing standard hygienic precautions, and especially by enforcing hand hygiene.
- Organizational or spatial contact isolation of VRE patients is mandatory in risk areas/at-risk patients.

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REVIEW ARTICLE

Control of the Spread of Vancomycin-Resistant Enterococci in Hospitals

Epidemiology and Clinical Relevance

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