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REVIEW

Vancomycin-resistant enterococci (VRE): a reason to isolate?

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Abstract
In recent years, an increase in invasive VRE infections has been reported worldwide, including Germany. The most common gene encoding resistance to glycopeptides is VanA, but predominant VanB clones are emerging. Although neither the incidence rates nor the exact routes of nosocomial transmission of VRE are well established, screening and strict infection control measures, e.g. single room contact isolation, use of personal protective clothing by hospital staff and intensified surface disinfection for colonized individuals, are implemented in many hospitals. At the same time, the impact of VRE infection on mortality remains unclear, with current evidence being weak and contradictory. In this short review, we aim to give an overview on the current basis of evidence on the clinical effectiveness of infection control measures intended to prevent transmission of VRE and to put these findings into a larger perspective that takes further factors, e.g. VRE-associated mortality and impact on patient care, into account.

Keywords Enterococci · Vancomycin · Vancomycin-resistant · Isolation · Infection control · Screening

Enterococci are Gram-positive bacteria that colonize the human gut in large numbers. Two subspecies of enterococci are of particular relevance in this context: *Enterococcus faecalis* and *Enterococcus faecium*. The two have clinically relevant differences in their susceptibility to antibiotics: while *E. faecalis* is usually sensitive to ampicillin, this is not the case for *E. faecium*, with a high proportion being resistant to beta-lactams. Treatment of these infections usually requires a glycopeptide (vancomycin or teicoplanin).

Recently, increasing numbers of infections with vancomycin-resistant *E. faecium* (VRE) have been observed. In Europe, this trend is most pronounced in central, southern and eastern Europe, where between 10 and 50% of all *E. faecium* isolates were reported to harbor resistance towards vancomycin, based on recent surveillance data [1, 2]. The most common gene encoding resistance to glycopeptides is VanA, but predominant VanB clones are emerging [3]. The spread of VRE poses a problem, as only few second-line antibiotics are available for the therapy of VRE infections, i.e. daptomycin and linezolid, neither of which is licensed for this indication.

Typically, patients with VRE infections have experienced intensive pre-treatment with antibiotics and present with multiple co-morbidities, e.g. organ transplant, kidney failure requiring dialysis, hematological and oncological disorders or prolonged intensive care stays [4–7]. The most common infections caused by VRE are bloodstream infections, central venous catheter-associated bloodstream infections and intra-abdominal infections. Colonization of the gastrointestinal tract with VRE regularly precedes invasive infection [8].

To this day, the impact of VRE infection on mortality remains unclear, with current evidence being weak and contradictory [9, 10]. Enterococci are less virulent in nature than *Staphylococcus aureus* or Gram-negative bacteria. Thus, invasive VRE infections mainly occur in hosts who are severely affected by a deteriorating underlying medical condition. The overall outcome of the patient is often determined by the underlying condition itself, and VRE infection may be a final event in subjects with a very poor prognosis.

In recent years, an increase in invasive VRE infections has been reported worldwide, including Germany [2, 11, 12]. However, for reasons unknown, there is significant variation in local and regional incidence rates. This development

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has drawn considerable attention to the topic of VRE infection as such and prompted a controversial discussion on how to best prevent them. Most measures aimed to stem the epidemic have focused on classical methods of infection control.

Enterococci are particularly resilient and can survive for prolonged periods on inanimate surfaces [13]. Therefore, it is not surprising that transmission of VRE has been described in hospitals [14]. However, it remains to be determined, which proportion of VRE colonization can be directly linked to transmission in the health care setting. Although neither the incidence rates nor the exact routes of nosocomial transmissions of VRE are well established, screening and strict infection control measures, e.g. single room contact isolation, use of personal protective clothing by hospital staff and intensified disinfection of environmental surfaces near colonized individuals, are implemented in many hospitals.

So, if the effectiveness of such measures on infection control for VRE is questionable, do at least individual patients benefit from them? One might argue that an approach of identifying colonized patients early on might facilitate effective treatment for VRE, as soon as the patient shows signs of infection. However, this does not seem to be the case. Only a very small proportion of patients colonized with VRE actually progress to infection. For example, among intensive care patients, only around 1% of those colonized develop VRE infection. It should, however, be pointed out that data in this population are scarce with most available data stemming from Taiwan. In hematological and oncological patients with a broad range of conditions, this rate is estimated at 1.5%. In contrast, hematological/oncological patients in high-risk settings, such as allogenic transplant, displayed a much higher risk with an overall rate of 14.0%. However, all analyses concerning this high-risk population stem from North American hospitals, where VRE incidence rates are traditionally high (Table 1).

Based on these data, detection of VRE in feces in combination with clinical signs of an infection would in most cases prompt unnecessary empiric treatment with compounds directed against VRE, i.e. daptomycin or linezolid. Therefore, this strategy would contradict general principles of antimicrobial stewardship. It is unquestionable that these drugs need to be administered in case of a clinically relevant infection, e.g. a bloodstream infection, but this situation needs to be differentiated from mere colonization. Moreover, there are no data showing that patients with VRE colonization benefit from empiric VRE therapy compared to targeted treatment as soon as the pathogen has been identified.

Is colonization at least preventable through infection prevention measures such as gowns, gloves, environmental cleaning or single room isolation? From 2006 onwards, a bundle of infection control measures, including improved cleaning, screening, a patient transfer stop and cohorting was implemented in a French 23,000-bed multi-hospital institution. These measures were followed by a very moderate decrease by 0.7 VRE cases per months. However, since a large bundle was implemented, it is impossible to determine the impact of each single component. Furthermore, a complete transfer stop for colonized patients may not represent a feasible option for all medical situations [28]. However, much can be learned from the reverse set-up: the abandonment of specific infection control measures implemented to prevent VRE transmission. In 2013, a large randomized controlled trial in intensive care units showed that untargeted decolonization of all patients by use of chlorhexidine, without screening and contact isolation for MRSA, was superior to a strategy of screening and contact isolation only or targeted decolonization of colonized subjects [29]. This study led to several large US medical centers stopping their isolation policies for MRSA and even VRE despite local laws requiring isolation [30–32]. The effects of the cessation of specific infection control measures on VRE (and MRSA) rates have recently been published in a series of papers and summarized in a meta-analysis [33]. The results can be summed up very simply: no negative effects have been documented. To the oversight of the authors, there are no published data available that demonstrate increased rates of VRE after cessation of specific infection control measures. The meta-analysis even comes to the conclusion that after the cessation a decreased rate of VRE infections and transmissions could be observed [33]. This is entirely plausible, as in the involved centers' routine infection prevention measures such as strict hand hygiene and decolonization of patients with chlorhexidine were reinforced.

The authors' conclusion to be drawn from this real-life experiment is that expensive measures such as screening and isolation can be abandoned in lieu of optimized general infection control efforts. These studies also underline the concept that general or "horizontal" measures of infection control are more appropriate compared to "vertical" measures, i.e. methods, which are directed against specific pathogens only [34].

Recent findings suggest that there may still be significant infection control potential in environmental cleaning. While it was shown that recent VRE isolates are increasingly tolerant to alcohol-based hand rubs [35], another study reported termination of a VRE outbreak after environmental cleaning by use of hydrogen peroxide vapor was included into an infection control bundle [36]. Again, as this measure was part of a bundle, its individual effect cannot be determined; however, the use of alternative environmental disinfectants seems to merit further assessments.

Another often ignored aspect is the potential of infection control measures to cause harm to patients. Several studies have shown that isolation is associated with many negative

Table 1 Incidence of VRE colonization and bloodstream infections (BSI) in high-risk patients

Population	Study period	Country	Incidence (%)			References
			Colonization	BSI	BSI in colonized patients	
Intensive care unit						
ICU adult	1997–2001	Taiwan	816/4538 (18.0)	6/4538 (0.1)	6/816 (0.7)	Yeh Microb Drug Resist 2004 [15]
ICU adult	2012–2014	Ireland	30/157 (19.1)	1/157 (0.6)	1/30 (3.3)	McDermott ICHE 2018 [4]
ICU pediatric	2013–2015	India	37/198 (18.6)	1/198 (0.5)	1/37 (2.7)	Amberpet J Lab Physicians 2018 [16]
Overall			883/4893 (18.0)	8/4893 (0.2)	8/883 (0.9)	
Hematology/oncology (HO) with a broad spectrum of underlying conditions						
HO	2008–2009	Germany	51/513 (9.9)	1/513 (0.2)	1/51 (2.0)	Liss Infection 2012 [17]
HO	2009–2010	South Korea	–	24/1587 (1.5)	–	Cho BMC Infect Dis 2013 [10]
HO	2010–2012	Turkey	50/126 (39.7)	2/126 (1.6)	2/50 (4.0)	Gedik J Infect Dev Ctrl 2014 [18]
HO	1998–2011	USA	–	48/2581 (1.9)	–	Rosko Leuk & Lymph 2014 [5]
HO	2016	Germany	501/3079 (16.3)	6/3079 (0.2)	6/501 (1.2)	Biehl ECCMID 2018 [19]
Overall			602/3718 (16.2)	81/7886 (1.0)	9/602 (1.5)	
Hematology/oncology (HO) in high-risk settings						
Allogeneic SCT	2008–2009	USA	68/247 (27.5)	23/247 (9.3)	13/68 (19.1)	Kamboj BBMT 2010 [20]
AML induction	2000–2008	USA	–	37/350 (10.6)	–	Ornstein Leuk & Lymph 2015 [21]
Allogeneic SCT	1997–2011	USA	–	76/800 (9.5)	–	Tavadze BMT 2014 [22]
Allogeneic SCT	2004–2008	USA	173/752 (23.0)	50/752 (6.6)	25/173 (14.5)	Vydra CID 2012 [23]
AML/ ALL induction	2006–2012	USA	82/214 (38.3)	15/214 (7.0)	12/82 (14.6)	Ford ICHE 2015 [24]
Autologous SCT	2006–2014	USA	108/300 (36.0)	9/300 (3.0)	9/108 (8.3)	Ford Transpl Infect Dis 2015 [25]
Allogeneic SCT	2007–2011	USA	–	39/238 (1.4)	–	Satlin Leuk & Lymph 2014 [26]
AML induction/SCT	2006–2014	USA	274/650 (42.2)	43/650 (6.6)	43[a]/274 (15.7)	Webb CID 2017 [7]
Allogeneic SCT	2004–2014	USA	96/203 (42.3)	11/203 (5.0)	10/96 (10.4)	Hefazi Transpl Infect Dis 2016 [27]
Overall			801/2366 (33.9)	303/3754 (8.1)	112/801 (14.0)	–
Overall for all populations			2256/10,820 (20.9)	391/16,376 (2.4)	128/2256 (5.7)	–

VRE vancomycin-resistant enterococci, *BSI* bloodstream infection, *ICU* intensive care unit, *HO* hematology/oncology, *SCT* stem cell transplantation, *AML* acute myeloid leukemia, *ALL* acute lymphatic leukemia

[a]This publication does not contain data on how many patients with VRE BSI had been previously colonized. We assumed that all BSI occurred in colonized patients

effects in this regard. For example, the quality of clinical care declines, and therapeutic as well as diagnostic procedures are postponed for infection control reasons [37–39]. Thus far, the impact of these negative effects on medical outcome of patients is not well documented. However, studies dealing with this issue raise concerns, that these effects may not be negligible. A recent study from the US showed that medical complication rates increase in isolated patients [40]. In addition, stigmatization and negative psychological effects can be observed. Once a patient is labeled as VRE carrier, this label remains with him or her as there is currently no standardized eradication procedure.

In summary, the available evidence does not support isolation as an effective tool to reduce clinically relevant VRE infections. An intervention that is not supported by clear evidence as to its effectiveness, but has been shown to have negative effects on patient outcomes should not be defined or even mandated as routine clinical practice. Rather, it should

be implemented under strict study conditions only, to generate the urgently needed evidence in the field. In infection control, as well as in all other specialties of medicine, the overriding principle should read: first do not harm.

Compliance with ethical standards

Conflict of interest LMB has received lecture honoraria from Astellas and Merck/MSD, and travel grants from 3M and Gilead. MJGTV is a consultant to: Alb-Fils Kliniken GmbH, Arderypharm, Astellas Pharma, Berlin Chemie, DaVolterra, MaaT Pharma and Merck/MSD; has served at the speakers' bureau of: Astellas Pharma, Basilea, Gilead Sciences, Merck/MSD, Organobalance, Pfizer; received research funding from: 3M, Astellas Pharma, DaVolterra, Gilead Sciences, MaaT Pharma, Merck/MSD, Morphochem, Organobalance, Seres Therapeutics.

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