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Vancomycin-resistant enterococci: an ongoing challenge for infection control

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Enterococci are part of the normal human flora. *Enterococcus faecalis* und *Enterococcus faecium* are the most common species isolated from human infections. Vancomycin-resistant enterococci (VRE) have emerged as a major cause of nosocomial infection as early as 1986 [1]. 10 years later, >15% of nosocomial enterococcal infections in United States hospitals were due to VRE, and even higher in intensive care units. *E. faecium* is the most commonly identified species identified. Enterococci are inherently resistant to many antibiotics, in particular to all cephalosporins. Today, >80% of all strains of *E. faecium* are ampicillin-resistant in Switzerland (www.anresis.ch), and approximately 5% are VRE. In contrast, *E. faecalis* remains susceptible to ampicillin in 97%, and detection of VRE among *E. faecalis* is rare. VRE belong to the multiresistant pathogens that rapidly spread and are difficult to treat [1, 2] Inducible vancomycin resistance in enterococci is due to a sophisticated mechanism that combines synthesis of cell wall peptidoglycan precursors with low affinity for glycopeptides and elimination of the normal target precursors.

Similar to other multiresistant pathogens, VRE was observed in Europe, and in 1994, VRE were first isolated in Switzerland [3, 4]. Vancomycin resistance is seen in addition to ***E. faecium*** and ***E. faecalis***, but also has been recognised in ***E. raffinosus***, ***E. avium***, ***E. durans***, and several other enterococcal species. Several genes, including *van*A, *van*B, *van*C, *van*D, and *van*E, contribute to resistance to vancomycin in enterococci. Multiple epidemics have been described with VRE, predominantly with genotype *vanA*.

Phenotype VanA and VanB are common in the USA, but phenotype Van C appears to be more prevalent in Europe (table) [5, 6]. The emergence and spread of VRE VanC in Europe is related to the use of the growth promoter avoparcin in animal husbandry. Avoparcin is a glycopeptide produced by ***Streptomyces candidus***, closely related to vancomycin. It was banned in 1997, and subsequently, VRE VanC decreased in European hospitals. Knowledge of the type of resistance is critical for infection control purposes: *van*A or *van*B genes are transferable and can spread from organism to organism.

New screening plates such as chromID™ VRE detect VanA and Vanc B enterococci, but inhibit growth of VanC enterococci. Enterococci of *van*C phenotype are not transferable, have been associated less commonly with serious infections, and have rarely caused outbreaks. In fact, our own data clearly indicate that the low risk for transmission of VRE of phenotype VanC does not justify contact isolation [7].

Many hemato-oncology patients are only colonised with VRE, that precede bloodstream infections [8]. VRE is

Table 1: Clinically important vancomycin-resistant enterococci.

Phenotype	**VanA**	**VanB**	**Intrinsic resistance, low level, type VanC1/C2/C3**
Species	*E. faecium* *E. faecalis*	*E. faecium* *E. faecalis*	*E. gallinarum* *E. casseliflavus* *E. flavescens*
MIC, mg/L vancomycin teicoplanin	64–100 16–512	4–1,000 0.5–1	2–32 0.5–1
Conjugation	Positive	Positive	Negative
Mobile genetic element	Tn*1546*	Tn*1547* or Tn*1549*	…
Expression of resistance	Inducible	Inducible	Constitutive
Location	Plasmid	Plasmid	Chromosome
Modified target	D-Ala-D-Lac	D-Ala-D-Lac	D-Ala-D-Ser
Associated with epidemics	Yes	Yes	No
Acquisition	Nosocomial	Nosocomial	Community, mainly food chain

Note: D-Ala-D-Lac, D-alanine-D-lactate; D-Ala-D-Ser, D-alanine-D-serine.
Adapted from courvalin P (10)

emerging as the most common cause of pre-engraftment bacteremia in patients undergoing allogeneic stem-cell-transplantation, and is associated with substantial mortality. Treatment options for VRE are very limited, especially for ampicillin-resistant *E. faecium* [9]. Daptomycin and Linezolid remain active, but emergence of resistance has been observed, and both antibiotics are very expensive.

In contrast to gram-negative bacteria, VRE extensively contaminates the environment: bedrails, floors, linen, in VRE patient rooms, but also keyboards of computers, and medical devices are commonly positive on wards with VRE patients. The Centers for Disease Control and Prevention (CDC) in Atlanta, USA, established guidelines to prevent transmission of VRE in 1995. This recommendation includes screening of high-risk patients such as those admitted to a hematology-oncology unit and contact isolation of carriers. Outbreaks in Zurich published in this journal by Thierfelder and collegues [11] and more recently in Lausanne clearly show that VRE remains a continuous threat to patients, especially for hematology- oncology patients. Once colonised, patients remain colonised for prolonged period of time, months to years. Since the environment of the patient room is heavily contaminated, and requires daily disinfection of the surfaces. The risk for a patient to acquire nosocomial VRE depends on the level exposure, expressed by number of colonised patients and area of contaminated surfaces.

The risk to acquire nosocomial VRE depends on several factors [10]

1. Colonisation pressure, defined as prevalence of patients colonized or infected at a given time period.
2. Glycopeptide, especially vancomycin use and subsequent antibiotic pressure on enterococci.
3. Level of infection control activities
   a. Screening of high risk patients;
   b. Compliance and speed of contact isolation of colonised patients;
   c. Environmental control by routine disinfection of patient area.

As a rule of thumb, VRE strains isolated from a clinical sample in the routine microbiology laboratory usually indicates that 10 other patients on that ward are colonized if they would be screened. Therefore, one clinical isolation of VRE should always prompt a large epidemiological work-up that includes an epidemiologic curve, screening of patients in contact with the index case, and molecular typing of these strains. Our own data (unpublished) show that it takes less than a couple hours for recontamination with enterococci even after a thorough disinfection of a ward. Patients may remain colonised for months and even years. Therefore, as the example of the outbreaks in Lausanne showed in 2011, a long-term intervention is necessary to stop such outbreaks. At the University Hospital of Basel, such a large-scale intervention in 1999 stopped a cluster, and nosocomial VRE were no longer detected >10 years despite active screening with enrichment cultures. VRE control is feasible, but takes a lot of effort, stamina, and restriction of vancomycin use, strict contact isolation of colonised patients, environmental control and sometimes even closure of a ward. Only large-scale interventions are successful, limited targeted activities are futile and not cost-effective in the long-term. The examples from Zurich and more recently from Lausanne support this statement.

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