VANCOMYCIN RESISTANT ENTEROCOCCUS (VRE)

By

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VANCOMYCIN RESISTANT ENTEROCOCCUS (VRE)

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Vancomycin Resistant Enterococcus (VRE) has been an increasing problem in the United States since the late 1980's. The cause is believed to be the use of oral vancomycin to treat diarrhea in the acute care setting. The most common infections are bacteremias, urinary tract infections, intra-abdominal, pelvic and wound infections. High risk patients are the immunocompromised, such as those with transplants, chronic renal failure, or diabetes. Other risk factors listed by the Center for Disease Control and Prevention (CDC) are exposure to antibiotic use, the health care system and advanced age. The bacteria have an intrinsic and acquired type resistance against several antibiotics. The acquired resistance type has the ability to share its genes with other organisms, such as Staphylococcus Aureus. This transfer, although presently very rare, presents a potential huge public health threat. Currently, only two drugs are approved by the Food and Drug Administration (FDA) for the treatment of VRE infection, quinupristin/dalfopristin and linezolid, and both are very expensive. The bacteria can either colonize or infect an individual. Colonization is when the bacteria is in the body, but does not cause an illness, as in the case of an infection. Diagnosis of VRE is made by blood, wound or stool cultures, or rectal swabs. The most common form of transmission is from one patient to another via the hands of a health care worker (HCW). The most
important preventative measure is by maintaining good hand hygiene, preferably by using an alcohol based hand rub, or antimicrobial soap.

Presently there is no mandatory reporting regarding VRE colonization or infection. There are no recommendations regarding the screening of HCWs for colonization (e.g. carrier status). Health care costs are rising, and there are few approved antibiotics for treatment, and aggravated to this is the lack of development and research of new antibiotics. The elderly is an increasing proportion of the U.S. population and the incidence of obesity is on the rise, which may indirectly lead to an increase of immunocompromised patients in the future. The following paper addresses the need to institute a mandatory reporting system, the need for the development of a task force involving federal, state and private institutions to address this pressing issue. Individual health care facilities need to develop a policy on how to test, assign and proceed with a VRE positive employee to prevent transmission and protect the patients. Other recommendations are to include VRE reporting and infection rates in the accreditation process for the Joint Commission on Accreditation of Healthcare Organizations (JCAHO), and for the CDC to convene its Hospital Infection Control Practices Advisory Committee (HICPAC) and update its recommendations. The nurse practitioner is valuable as an educator of this pressing issue, not only for the patients, but for other staff members and the public. As advocates for their patients, the nurse practitioner can work for changes in the health care system to address the need for more affordable and new antibiotics, need for research and development, as well as policy changes to include mandated reporting of all multidrug resistant organisms, not only VRE.
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Introduction

Vancomycin Resistant Enterococcus (VRE) has become endemic in acute care and long term care facilities since the first case presented in 1986. Presently, it is mainly a problem in acute care and long term care settings, but is also of interest for primary care providers as increasing numbers of patients colonized with VRE are released into the community. The Center for Disease Control and Prevention (CDC) has recognized this problem and deemed it as a serious threat to the public’s health. Unfortunately there is very little found in the nursing or scientific literature addressing this serious problem. Consequently this paper presents for health care workers (HCW) the background, risk factors, epidemiology, treatment and prevention of VRE. A discussion will follow with recommendations including an education tool designed for HCW in the acute care setting. This tool may be printed as a poster and displayed for educational purposes.

History

Vancomycin has been used since the 1950’s to treat serious gram positive infections. VRE was first reported in the U.S. in 1986 and is presently a worldwide problem on six continents (Hayden, 2000). The primary cause in the U.S. is believed to be the use of oral vancomycin to treat antibiotic-associated diarrhea in the acute care setting (Rice, 2001). Bodaruk et al. (2001) examined 12 meat processing plants in the U.S. and found no enterococcal isolates, which supported the assumption VRE in the U.S. primarily is contracted though contact with the health care system. Contrary to this, in Europe the glycopeptide, avoparcin was used as a growth promoter in farm animals and VRE has was found in the gastrointestinal (GI) tract of farm animals, and in processed meats. Healthy individuals who ate these meat products carried VRE in the GI
tract and VRE was most likely contracted via contaminated meat products (Muto et al., 2003).

**Biology**

Enterococcus is part of the normal intestinal flora in humans and animals. Vancomycin resistance in enterococcus is of the intrinsic and acquired type. The intrinsic type has an inherent, low level resistance or tolerance towards vancomycin, cephalosporins, penicillinase-resistant penicillins, aztreonam, clindamycin, trimethoprim-sulfamethoxazole, and aminoglycosides. Exposure to these antibiotics inhibits the growth of enterococcus (Donskey et al., 2003). Acquired resistance can be transferred from one bacterium to another via plasmids and transporons (Abuhammour et al., 2002). Antibiotic resistance takes place when a microbe acquires a gene, which enables the microbe to inactivate, or nullify the antibiotic’s antimicrobial activity (Muto, 2003).

To date, the VRE bacteria have been able to share their genetic material with Staphylococcus (S.) Aureus (Willems et al., 2005). Eight cases of Vancomycin Intermediate S. Aureus (VISA) and two cases of Vancomycin Resistant S. Aureus (VRSA) have been reported in the U.S. (CDC, 2003). VRSA may be the next global crisis in antimicrobial resistance (Willems et al., 2005).

There are 17 or more species of enterococcus. Enterococcus (E.) faecalis and E. faecium are the most common to infect humans. Occasionally E. raffinosus, E. casseliflavus, E. durans, or E. avium can cause human infections (Abuhammour et al., 2002). E. faecium, usually containing the vanA gene is the most common VRE in U.S. hospitals (CDC, 2005b). E. faecalis is more pathogenic than E. faecium (Rice, 2001).
VRE colonization of an individual occurs when the VRE bacteria is present in the body, but does not cause an illness. VRE infection is when the bacteria do cause an illness (CDC, 2000). Donskey et al. mentions a study in Cleveland where colonization rates versus infection was 10 to 1 (2003). Murray states the GI tract is the most common site of colonization, but skin surfaces are also common (2000).

**Epidemiology**

VRE is not a reportable illness in Oregon, Washington; or to the CDC. Health care facilities and other agencies are able to keep their VRE infection rates hidden from public scrutiny. Data available tend to be old, and on other occasions limited anecdotally to the intensive care unit (ICU) patient population. The National Nosocomial Infections Surveillance (NNIS) System Report is a national database where approximately 300 hospitals in the U.S. voluntarily submit data regarding their nosocomial infection surveillance data. The report issued in October 2004 stated that the VRE infection rate in ICU patients from January to December 2003 was 28.5%, a 12% increase from the period 1998 - 2002 (NNIS, 2004).

**Enterococcus** is the second most common nosocomial infection in the U.S. Between 1989 and 1993 VRE increased 20 fold, from 0.3 to 7.9% (Abuhammour et al., 2002). The CDC (2000) reports VRE is one of the most common multidrug resistant organisms in patients living in non-hospital healthcare facilities, but does not provide epidemiological data. It is unclear what percentage VRE is of all enterococcal infections. Willems et al. propose VRE is more than 25% of all enterococcal bloodstream infections in hospitalized patients in the U.S. (2005).
Common infections caused by enterococci are endocarditis, bacteremia, urinary tract infections (UTI), pelvic, intra-abdominal and wound infections. UTI, more frequent in women, are the most common problem caused by enterococcal infection and are usually acquired nosocomially. Community acquired enterococcal bacteremia are more common than nosocomial, 36% versus 0.8%. In most cases, E. faecalis is the cause of enterococcal bacteremia with men having a higher incidence than women (Donskey et al., 2003). The elderly have an increased incidence of enterococcal bacteremia (Abubammour et al., 2002).

Risk factors

Nguyen categorizes risk factors for colonizing pathogens into three areas such as iatrogenic, organizational, and patient risk factors. Iatrogenic risk factors are: invasive procedures, antibiotic use, and indwelling vascular lines. Contaminated water and air conditioning systems, staffing (nurse-to-patient ratio) and physical layout of the facility are examples of organizational risk factors. Patient risk factors are severity of illness, underlying immunocompromised state and length of stay. As soon as the patient is admitted to a health care facility, colonies of hospital strain bacteria appear on the patient’s skin, in the respiratory and genitourinary tract (2004).

The CDC lists risk factors for colonizing pathogens as being previous exposure to antimicrobial agents, invasive procedures and devices, advanced age, previous contact with the health care system and previous colonization with multidrug resistant organisms. Other risk factors are severity of illness, and underlying diseases, such as diabetes, chronic renal disease, peripheral vascular disease and dermatitis, or other skin lesions (2000).
Exposure to antibiotics active against anaerobic bacteria, which are the primary competitors of enterococci for the colonization of the GI tract, and antibiotics inactive against enterococci favor colonization and produce high VRE levels in the stool. Exposure to extended spectrum cephalosporins and similarly active beta-lactams are other risk factors for colonization and infection (Rice, 2001). Other risk factors for colonization found by Bonten et al. in a study of 181 patients during 19 weeks in a medical ICU were the proportion of patients in the unit who were colonized, enteral feeding, and the use of sucralfate and antibiotics, especially third generation cephalosporins (1998).

The CDC states healthy individuals are at low risk for VRE infection, but there is no information on risks for colonization (2000). Further research is needed to explore these important issues as the list of risk factors continues to grow.

**Diagnosis**

The CDC’s Hospital Infection Control Practices Advisory Committee (HICPAC) recommends screening by rectal swabs or stool cultures. In addition, cultures may be taken from wounds, blood, urine or other body sites and tested for VRE. The frequency of screening should be based on the size of the population at risk and the hospital involved. Routine screening of high risk patients can detect VRE and efforts to prevent spread can be instituted. All enterococcal isolates in a facility where VRE has been previously identified should be tested for VRE (1995). More specific guidelines on how many patients, a proportion or all high risk patients, or the possibility of screening low risk patients are needed.
Isolation of VRE bacteria from a blood culture or other normally sterile site confirms diagnosis of VRE colonization (Abuhammour et al., 2002). Routine or random rectal swabs, or stool cultures will confirm colonization, but low levels of VRE may not be detected in rectal swabs. These patients may be sources for further transmissions (Weinstein, 1999). According to Oregon Health Sciences University (OHSU) core lab the cost to process one rectal swab for VRE is $60 (personal communication, Nov. 2005).

Treatment

Two drugs, Quinupristin/dalfopristin (Synercid) and Linezolid (Zyvox) are approved by the Food and Drug Administration (FDA) to treat VRE infections. Although not approved by the FDA, treatment of VRE can be with off-label prescribing of other drugs such as daptomycin, nitrofurantoin, chloramphenicol, penicillin, ampicillin or other antibiotics depending on the susceptibility of the isolated strains. Health care providers should consider the severity of the infection and susceptibility to other antibiotics when choosing treatment (Donskey et al., 2003).

Quinupristin/dalfopristin and linezolid are the two primary medications for treating VRE. Quinupristin/dalfopristin is approved for patients 16 years and older to treat serious bacteremia caused by E. faecium. It is not effective against E. faecalis infections (Abuhammour, 2002). The main side effects for quinupristin/dalfopristin are arthralgias, pain and inflammation at infusion site. Bacterial resistance has developed against the drug; in New York resistance was reported having increased from 8.3% in 2000 to 18.4% in 2001 (Muder, 2003).

Linezolid is effective against both E. faecium and E. faecalis infections. Possible side effects for linezolid are GI disturbance, nausea, rash,
thrombocytopenia and anemia (Muder, 2003). Bacterial resistance against linezolid has also emerged (Donskey et al., 2003).

According to J. Bubalo, Pharm. D. (personnel communication, Oct. 2005) at OHSU the average wholesale price for quinupristin/dalfopristin is $132 for one 500 mg vial administered intravenously (IV). Linezolid costs $110 for one 600 mg tablet and $85.50 for one IV bag. Length of treatment depends on the condition and diagnosis of the individual patient. Treatment for bacteremia and pneumonia is approximately 14 days, wound and severe soft tissue infections about 2-3 weeks, and osteomyelitis anywhere from 6 -12 weeks.

Quinupristin/dalfopristin can only be given IV and standard dose is 7.5 mg/kg IV q 8 hrs. Linezolid is dosed once a day at 600 mg either PO or IV. A referral for consultation with an infectious disease specialist is recommended when treating VRE infections (Sanford Guide to Antimicrobial Therapy, 2005).

It is difficult to estimate the cost of VRE, but one study estimated that VRE bloodstream infections on an oncology ward increased the length of stay 13.7 days per patient. Improved infection control measures on this ward led to savings of $189,318 for one year (Montecalvo et al., 2001).

It is not recommended to treat people who are colonized with VRE (Weinstein, 1999). One study in 1999 evaluated attempts to de-colonize patients in a Toronto hospital. VRE positive patients (n=39) were divided into two groups. One group of 15 subjects was given both oral bacitracin and doxycycline, and the other group was given placebo tablets. Initially the group receiving medication tested negative on stool cultures, but after 30 days there was no difference between the treatment and the placebo group.
After the drugs were stopped several in the treatment group relapsed with VRE stool levels higher than before treatment (Weinstein, 1999). Weinstein concluded bacitracin and doxycycline are effective in suppressing VRE, but the effect is transitory (1999).

Prevention

Hand washing is the single most important measure to prevent nosocomial infections. Most VRE transmissions are from one patient to another via the hands of a HCW. VRE has been isolated remaining for 60 minutes on the hands of HCWs after inoculation. It is unknown if the bacteria can survive even longer (Bonten, 1998).

Alcohol based disinfectants have been shown to remove bacteria more effectively than antimicrobial soap, or bland soap and water. The length of contact with the disinfectant affects the effectiveness of bacterial elimination. Gloves do not eliminate the need for hand washing, as VRE has been found on the hands of HCWs after glove removal (Hayden, 2000). A study by Wendt et al. (1998) showed a variety of VRE strains survived for at least one week, and some for as long as four months on dry surfaces.

The CDC’s Action Plan recommends the appropriate use of antibiotics and prevention of infection transmission to prevent the spread of drug resistant infections. The CDC defines appropriate use as “use that maximizes therapeutic impact while minimizing toxicity and the development of resistance”. The correct antibiotics should be prescribed only when needed in the correct dose and duration (2005a).

The CDC’s HICPAC recommends that a VRE positive hospital patient be placed in a private room, the use of gloves by HCW, and if “substantial contact” with the patient or environmental surfaces in the room, a gown should be worn. Before leaving the room, the HCW should remove the gown and gloves and wash the hands with an antiseptic soap.
or waterless antiseptic agent (1995). In long term care facilities or other non-hospital facilities it is recommended to place the colonized patient in a private room if possible or if not, cohort colonized patients. If proper precautions are taken, such as covering draining wounds and containing bodily fluids, patients may participate in group activities. In dialysis centers the colonized patient should be placed in corners with as few adjacent stations as possible (CDC, 2000). The CDC recommends that in-home caregivers practice good hand hygiene, use towels only once, change and wash linen on a routine basis, and use gloves when in contact with bodily fluids and wounds (2000).

CDC does not recommend pre-admission screening for patients admitted to health care facilities, but screening of high risk patients upon admission may decrease VRE transmission (2000). Screening of HCWs is not commonly done in the U.S., but has been done in Europe with decreased transmission rates (Muto, 2003). VRE colonized HCWs or others may be covered under the American with Disabilities Act, or other state or local law (CDC, 2000).

Hayden recommends chart reviews to establish common links between colonized or infected patients and identify sources of transmission. Another approach is to practice universal gloving for all patient contact and care regardless of colonization or not (2000). Furthermore, the CDC recommends primary care providers be notified if a patient is known to be colonized, or infected (2000).

Discussion

Multidrug resistance is a worldwide problem and pertains to all HCW. The need and ability to treat infections is paramount to nurse practitioners as health care providers. Harbarth et al. (2005) contends that the increase in life expectancy, the susceptibility of
older individuals to infections, and an increase in immunocompromised patients may
increase indirect antimicrobial resistance. Of adults 65 years or older it is estimated at
least 80% have at least one chronic health problem and 50% have at least two. In
developed countries the health care costs for elders are three to five times greater than for
younger adults (High et al., 2005). Advanced age is one of the risk factors for VRE
(CDC, 2000). Type 2 diabetes mellitus is another risk factor identified by the CDC
(2000). Obesity is a risk factor for type 2 diabetes (Votey et al., 2005) and the CDC
estimates that 65% of adults are now overweight or obese (2005c).

The cost of general health care is on the rise and with the potential increase of
multidrug resistant organisms the treatment cost may go even higher. This is
compounded by the fact there are only two drugs, quinupristin/dalfopristin and linezolid,
specifically approved by FDA for the treatment of VRE infections and both drugs are
very expensive. Another problem is the development of bacterial resistance to these
drugs, which has already occurred (Donskey et al., 2003). Wenzel (2004) compares the
net present value (NPVR) i.e. the return in future dollars after adjustment for the
investment and any lost income, of new antibiotics of 100 with the NPVR of 1150 for
musculoskeletal drugs. Pharmaceutical companies which are profit driven will be more
likely to choose the drugs with the highest positive NPVR. The lack of development of
new drugs will further exacerbate the problem with multidrug resistance.

There are several deficits in our present system. VRE is not a reportable condition
and presently colonization and infection rates are unknown. The CDC’s HICPAC
consists of volunteer hospitals participating in reporting and no mandatory reporting
exists. The CDC’s recommendations for VRE were published in 1995. No update has
been done since, and later CDC recommendations on its website are based on these committee findings.

Cost for treatment is very high. The uninsured or underinsured seeking care most likely will not be able to fill a prescription amounting to hundreds, or thousands of dollars. While these problems exist already multidrug resistance and few antibiotics options will aggravate the situation.

Compliance with infection control measures is another problem. About 30-40% of resistant infections are transmitted from the hands of HCW (McGowan, 2001). In the Siouxland region of Iowa a taskforce involving 32 health care facilities together and the CDC was created when VRE was discovered in the late 1996. Aggressive infection control practices were implemented and the VRE prevalence decreased from 2.2% in 1997 to 0.5% in 1999 (Ostrowsky et al., 2001). It is possible to decrease VRE in health care facilities and our community.

There has been a successful effort in the past five to ten years, especially in the ambulatory setting, to reduce the number of antibiotics prescribed to those without a bacterial infection (Harbarth et al., 2005). In the community, the clinician may be tempted to liberally use antibiotics for short term benefits to the individual patient and not consider the long term disadvantage of antimicrobial resistance. Instead, the health care provider should only prescribe what is absolutely necessary and educate the patients about proper antibiotic use. Harbarth et al. (2005) contends educational programs involving both health care providers and the public have revealed promise in changing ways of thinking and behaviors.
Recommendations

It is necessary to institute a mandatory reporting system, either through the state or through the CDC. This would serve two purposes: one to ensure adequate public information of the problem and second to make the institutions aware and accountable for nosocomial infections and its spread. Another way to achieve information and compliance with infection control practices is through the accreditation process for the Joint Commission on Accreditation of Healthcare Organizations (JCAHO). If JCAHO is to grant accreditation, a minimum acceptable infection control and disclosure system should be in place.

For patient safety HCWs should be tested for colonization. The health care setting, hospital or non-hospital, should institute a policy and procedures on the placement of a VRE positive employee, and determine when to clear the employee (e.g. after two or three consecutive negative rectal swabs, or stool cultures). This policy could be part of the JACO accreditation process as well.

The CDC should convene a new HICPAC committee hearing. It has been ten years since the last published recommendations. The problem with increased multidrug resistance, including VRE has drastically increased since and a more recent recommendation is needed.

Another suggestion is to convene a National Institute of Health (NIH) task force consisting of the CDC, physicians, nurses, hospital and non-hospital health care facilities to address multidrug resistance. Volunteer participation would not negate the need for mandatory reporting as mentioned above. The Siouxland case confirms it is possible to reduce VRE prevalence.
Hospitals and other health care facilities need to immediately address improved housekeeping practices and prioritize their implementation, even if short term costs are higher. Additional staff, more effective cleaning solutions and supplies, and longer turn around times on patient bed availability could improve VRE transmission. The end cost will be higher if drug resistance continues to increase.

Health care providers with prescriptive privileges should continue to be prudent in the use of antibiotics, even if the individual patient may request them. The provider is in a position to educate the public of proper antibiotic use, and the consequences of multidrug resistance and its future dire implications.

Nurse practitioners are well suited to serve as educators for patients and other health care staff, physicians, registered nurses, aids, housekeeping staff, and others for this rather complex issue. This crisis not only involves VRE resistance, but the financial problems with high costs, and lack of research and development of new antibiotics. Education is needed for the potential threats of new or an increase in more virulent multidrug resistant organisms, such as VRSA. Nurse practitioners can be role models and educators of the importance of hand washing and compliance with infection control measures.

Nurse practitioners teach and encourage health promotion in their daily practice. In doing so, by promoting a healthy lifestyle the increasing proportion of elderly in our society may live healthier, and thus need fewer antibiotics to treat opportunistic infections. Nurse practitioners may indirectly contribute to a decrease in multidrug resistance, including VRE, by educating all patient populations regarding health promotion and disease prevention measures, such as appropriate weight management to
prevent obesity, one risk factor for diabetes mellitus. Nurse practitioners can advocate for changes in health care policy, and advocate for the vulnerable in our society, such as the uninsured or underinsured.
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Appendix A. Education Tool for all staff in the acute care setting.

VANCOMYCIN RESISTANT ENTEROCOCCUS (VRE).

WHAT IS IT?

It’s an enterococcal bacterium resistant to vancomycin and in most cases other antibiotics as well.

WHY IS IT IMPORTANT?

Vancomycin is an antibiotic used to treat serious infections. If we can’t use it we have lost an important option to treat and cure infections. VRE infections are very serious for our patients. The medications used to treat it are very expensive, and may prolong or complicate the patient’s recovery. In some cases, VRE infections can be fatal.

WHAT'S THE DIFFERENCE BETWEEN COLONIZATION AND INFECTION?

Colonization is when you have the bacteria in your body, but it’s not causing an illness.

There are many more colonized individuals than those with an infection. Healthy people, health care staff, and others can be colonized and not know about it.

Infection is when you have the bacteria and it’s causing an illness.

HOW DO YOU GET RID OF IT?

Colonization is not treated. The body has to rid itself of the bacteria. It may take weeks, or years.

Infection is treated with very expensive antibiotics. There are only two approved for VRE treatment, quinupristin/dalfopristin and linezolid. Linezolid costs about $110 per tablet and quinupristin/dalfoprisin only comes in intravenous form (IV).

HOW DO WE PREVENT IT?

Hand washing is the one of the most important measures we all can do. Using an alcohol based hand rub, or antimicrobial soap is the best. VRE bacteria have been shown to survive on health care workers’ hands for up to 60 minutes.

The most common way of spreading VRE is on the hands of health care workers from one patient to another.
Good housekeeping is essential. VRE bacteria have shown to survive on inanimate objects, such as bed rails, curtains, blood pressure cuffs, etc. for up to several weeks. VRE can then infect or colonize patients, visitors, and staff.

Adhere to isolation procedures and always wash hands before entering the VRE colonized patient’s room, use gloves, and a gown if touching the patient or surfaces in the room, and before leaving the room remove gloves, and gown and wash hands, preferably with an alcohol based hand rub, or antimicrobial soap.